The Journal of
Thoracic and
Cardiovascular Surgery

VOLUME 41
FEBRUARY 1961
NUMBER 2

Original Communications

EARLY SECONDARY THORACOTOMY FOLLOWING PULMONARY RESECTION

Frederick W. Marx, Jr., M.D., Los Angeles, Calif., and
John D. Steele, M.D., San Fernando, Calif.

IN THE TREATMENT of the complications of pulmonary resection, there are times when the pleural cavity must be re-entered early in the postoperative course. There is little in the literature in regard to the indications for and the results of such corrective secondary thoracotomies.

At the time of the initial operation, the patient's disease is the indication for surgery, and the original procedure is carried out at the time most propitious for the treatment of the original disease. Different considerations govern the secondary thoracotomy. The operation is not elective, but is an emergency or semi-emergency. In our series, patients were returned to the operating room and the thoracotomy wounds reopened in their entirety a few hours to 3 weeks after the original operation. It was not primarily the patient's disease which prompted the secondary operation, but rather complications of the initial pulmonary resection, air leak, bleeding, or infection. The inherent dangers in the procedure differ considerably from those of the initial thoracotomy. The patient's physiologic and defense mechanisms, already taxed by the recent thoracotomy and its complication, face major additional stresses. On the other hand, the problems facing the surgeon the second time are more straightforward; the simple suture of a bleeding point or an air leak, or the dissection of a small subsegment of infarcted lung parenchyma is expected to return his patient to an uncomplicated postoperative course.

From the Veterans Administration Hospital, San Fernando, Calif., and from the Department of Surgery, University of California, Los Angeles, Calif.
Received for publication Jan. 8, 1960.

TABLE I. PATIENTS REQUIRING SUBSEQUENT THORACOTOMY FOR HEMORRHAGE

CASE	DISEASE	INITIAL THORACOTOMY	REASON FOR SECONDARY THORACOTOMY	FINDINGS AT SECONDARY THORACOTOMY	IMMEDIATE COMPLICATIONS OF SECONDARY THORACOTOMY	LATE COMPLICATIONS
1. White male, age 38	4.5 cm. coccidioidal cavity	LU lobectomy, 6/19/56	Postoperative hemothorax	960 Gm. of clotted blood; source probably hilar nodes, 6/20/56	None	None
2. White male, age 30	Fibrocaseous tuberculosis	RU lobectomy, 10/15/57	Postoperative hemothorax	1,100 c.c. liquid and clotted blood from apical parietal pleural adhesions, 10/16/57	Recurrent hemothorax, 1,000 Gm. removed, 10/22/57, source undetermined	None
3. White male, age 25	Fibrocaseous tuberculosis	RU lobectomy, 4/14/59	Brisk hemorrhage and shock, night of surgery	Blood clots; source apical parietal pleural adhesions, 4/15/59 (1:A.M.)	None	None

We have analyzed the 20 secondary thoracotomies performed for the correction of the complications of pulmonary resection at the San Fernando Veterans Administration Hospital during the 4½ year period from July 1, 1955, to Dec. 31, 1959. Excluded from the series were other cases which required further procedures in the postoperative period for the treatment of complications such as reinsertion of intercostal tubes, small rib resections for drainage, and tailoring thoracoplasties. During this same period, 356 pulmonary resections were performed. In this pulmonary disease hospital, approximately two thirds of the pulmonary resections are performed for tuberculosis. There is a similar predominance of tuberculosis as the underlying disease in our secondary thoracotomies, but carcinoma, coccidioidomycosis, and bullous emphysema are also represented. Our 20 patients were all males, and all had had a pulmonary resection of some variety. The types of complications necessitating reoperation fall into three major categories: postoperative hemorrhage (3 cases), sepsis (2 cases), and air leak, either peripheral or from the bronchial stump (15 cases).

The surgeon, during the subsequent thoracotomy, is in a unique position to observe, culture, and biopsy areas of disease (iatrogenic or not) not usually visualized.

The major purpose of this review is the analysis of the indications for, and the surgical results of, our secondary thoracotomies.

SECONDARY THORACOTOMIES

Secondary Thoracotomies for Hemorrhage.—

Three patients had subsequent thoracotomies because of massive hemorrhage (Table I). A third operation was performed on 1 of these (Case 2) because of reaccumulation of blood 6 days after the secondary thoracotomy (Fig. 2, *B*). None of these patients had an antecedent history of bleeding. Routine preoperative blood studies, the minimum of which included bleeding time, coagulation time, and platelet estimations, were not considered significant.

In all 3 cases, secondary thoracotomy was done within the first 12 hours after the initial procedure. Diagnosis was obvious in the single patient (Case 3) who was in shock with considerable blood draining from the chest tubes. In the other 2 patients, the roentgenographic density on the operated side on the first postoperative day, plus the need of blood replacement on the day of operation, were the indications for re-exploration (Fig. 1 and Fig. 2, *A*).

At the time of subsequent thoracotomy, it is of interest that in none of the four procedures was a bleeding vessel of any appreciable size found. At re-exploration following a lobectomy for coccidioidomycosis (Case 1), the operator removed 960 Gm. of clotted blood and the most probable source of bleeding was a mass of lymph nodes near the hilum. In Cases 2 and 3, very small bleeding points on the parietal pleural surface where adhesions had previously been lysed were oversewn, and in the tertiary thoracotomy for recurrent hemothorax (Case 2), 6 days after the second procedure, no bleeding vessels were visualized.

Two of the 3 patients had no further difficulties after the secondary thoracotomies and, after the third operation in the other one, this patient also had an uneventful recovery. These cases illustrate our policy of performing subsequent thoracotomies for clotted hemothorax as a prophylaxis against fibrothorax and infection. Our experience with the use of enzymes in the treatment of massive hemothorax has been disappointing.

Secondary Thoracotomies for Sepsis.—

Two patients in our series were reoperated upon for sepsis (Table II). Our incidence of postoperative infection following thoracotomy is relatively low, and those cases in

TABLE II. PATIENTS REQUIRING SUBSEQUENT THORACOTOMY FOR SEPSIS

CASE	DISEASE	INITIAL THORACOTOMY	REASON FOR SECONDARY THORACOTOMY	FINDINGS AT SECONDARY THORACOTOMY	IMMEDIATE COMPLICATIONS OF SECONDARY THORACOTOMY	LATE COMPLICATIONS
4. White male, age 21	Tuberculosis with recent appearance of cavity while on chemotherapy	RU lobectomy, 6/8/59	Sepsis, not localized	Benign appearance of hemithorax; culture of hemolytic *Staphylococcus aureus*, coagulase positive, 6/19/59	None	Recurrence of sepsis with drainage of apical empyema, 7/9/59; recovery
5. Negro male, age 40	Tuberculosis with destroyed right lung	Rt. pneumonectomy, 11/12/58	Sepsis, not localized	Infected hemithorax due to nonhemolytic *Staphylococcus aureus*, 12/4/58; empyema drained	None	None—pleural cavity sterilized and allowed to refill

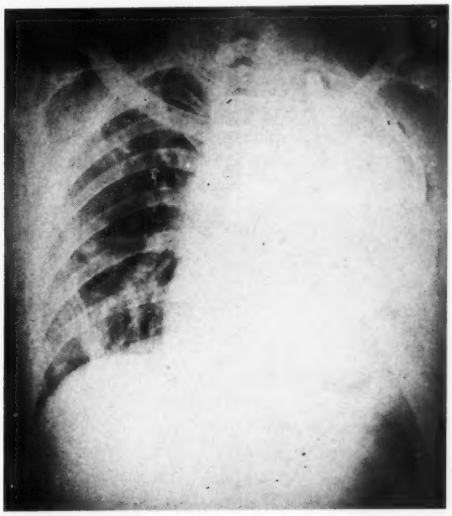
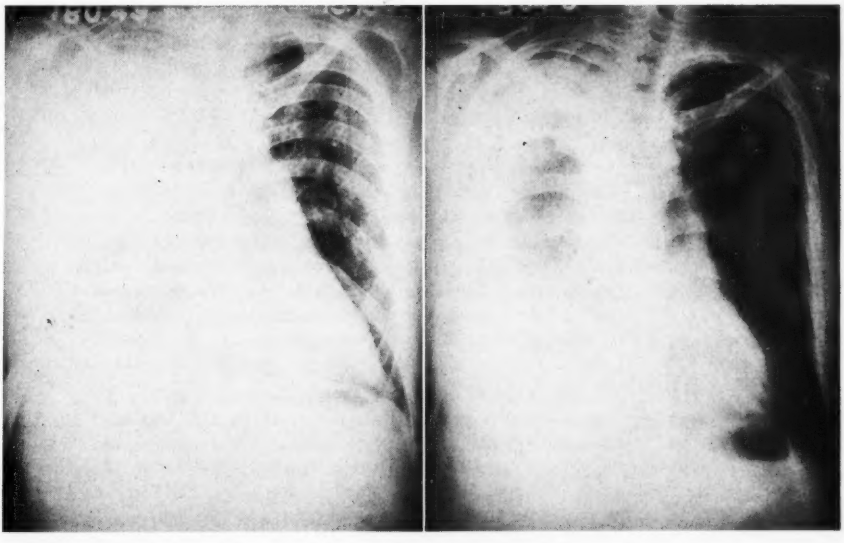


Fig. 1.—Case 1. Roentgenogram made 24 hours after initial thoracotomy which shows opaque hemithorax from hemorrhage.



A. *B.*

Fig. 2.—Case 2. *A*, Roentgenogram made 24 hours after initial thoracotomy which shows complete opacity on operated side, due to hemothorax.

B, Five days after secondary thoracotomy blood has reaccumulated which necessitated a third exploration.

which postoperative infection develops have rarely required more than a drainage procedure at the most. In Cases 4 and 5, however, the source of high fever and leukocytosis remained unexplained until the secondary thoracotomy. In Case 4, a patient who had a right upper lobectomy for pulmonary tuberculosis, the original drainage tube remained in place for 9 days because of a peripheral air leak which finally sealed. On the tenth day, his temperature rose to 103° F. and the white blood count to 38,000. Repeated thoracenteses of loculated spaces produced no fluid and little air, and no source of infection could be found elsewhere. He was returned to the operating room the following day for re-exploration.

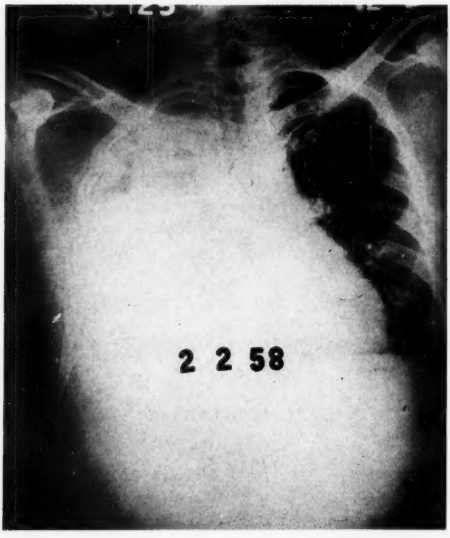


Fig. 3.—Case 5. Multiple fluid levels illustrating the difficulty in locating loculated infection by thoracentesis. At secondary thoracotomy, an empyema due to nonhemolytic *Staphylococcus aureus* was found.

The hemithorax did not appear grossly infected, but a routine culture taken from the pleural cavity yielded *Staphylococcus aureus,* coagulase positive. Postoperatively, the temperature remained normal during a period of intensive antibiotic therapy, but at its conclusion (18 days after the secondary thoracotomy) his temperature rose to 102° F., the white count to 23,000, and a fluid level appeared high in the right hemithorax. This localized empyema pocket was drained subsequently through the bed of a resected portion of the second rib. Culture of the pus revealed the same organism which had been found at the secondary thoracotomy. He recovered satisfactorily.

Case 5, a patient who had had a pneumonectomy for tuberculosis, presented a similar diagnostic problem. Although his immediate postoperative course was unremarkable, a low grade fever developed which, during the third week, rose to 103° F. The roentgenogram showed multiple fluid levels in the right pleural cavity (Fig. 3). Thoracentesis was not diagnostic but, at secondary thoracotomy, the pleural cavity was obviously infected, and a culture yielded nonhemolytic *Staphylococcus aureus,* coagulase negative. An open drainage was performed shortly afterward. The space was subsequently sterilized and allowed to refill, according to the method of Kent.[1]

Secondary Thoracotomies for Air Leak.—

Our most common postoperative complication requiring secondary thoracotomy was air leak (Table III). Four cases (Cases 6, 7, 8, and 9) represented the simplest type of problem. Cases 6 and 8 were patients who had had lobectomies but, in each instance,

the fissures were incomplete and the interlobar planes were developed in the same manner as in segmental dissections. In Case 6, a patient who had had a right upper lobectomy for cavitary coccidioidomycosis, the chest tubes had been removed 4 days after initial thoracotomy. A large pneumothorax developed 48 hours later. The lung failed to re-expand after replacement of the drainage tubes, and a secondary thoracotomy was performed. A 2 mm. bronchus on the surface of the middle lobe was found to be leaking. This was closed with a figure-of-eight suture, and the phrenic nerve crushed. Two days later, the chest tubes were removed and the patient's recovery was uncomplicated thereafter. Case 8, a patient on whom a left upper lobectomy had been performed for epidermoid carcinoma, had a secondary thoracotomy 16 days postoperatively for persistent air leak. Tiny leaks from needle holes on the lingular and anterior segmental bronchial stumps under the pleural flap were sutured, but air leakage persisted. Six days after the secondary thoracotomy, the tubes were withdrawn and needle aspirations started. Even though an air leak persisted, the space did not enlarge and because the prognosis was poor, the patient was discharged. Roentgenograms made 1 year later showed disappearance of the space.

The other 2 patients with the same type of air leak had had segmental pulmonary resections. A left apicoposterior segmental resection for tuberculosis (Case 7) was complicated by persistent air leakage and an incidental temperature elevation to 102 to 103° F. At reoperation, adhesions surrounding the lung were freed and three small air leaks in the intersegmental plane were oversewn. The patient's subsequent postoperative course was uneventful. A similar procedure 16 days after a left superior subsegmentectomy and upper lobectomy for tuberculosis (Case 9) resulted in cessation of air leak and an uneventful recovery. In this instance, a 2.0 mm. leak from a small bronchus on the surface of the superior segment was found and was oversewn.

All 4 of the patients just described had in common the fact that, at secondary thoracotomy, the remaining lung parenchyma appeared viable, and suture ligatures were used to close the leak. Three of the 4 had excellent immediate postoperative results, and in the fourth case (Case 8) the leak eventually sealed spontaneously. We believe that if the resected surface of the lung is allowed to come in direct contact with the parietal pleura, early in the postoperative course, sealing of air leaks is promoted. Possibly the lysis of early postoperative adhesions prohibiting this apposition is as responsible as the suturing of leaks in the success of secondary thoracotomy.

Another explanation for persistent air leak found at secondary thoracotomy has been pointed out by Salyer and Harrison.[2] They believed that inadvertent clamping of intersegmental venous channels causes thrombosis with resulting infarction. In their series, initial dissections were frequently difficult, and, to avoid leaving diseased areas behind, additional subsegments were removed. They speculated that this additional dissection may possibly have compromised the venous supply.

In 5 of our cases, persistent air leaks noted at secondary thoracotomy were present in infarcted subsegments. As in the preceding group of patients with air leaks, the initial procedures had been segmental resections of some variety, or a lobectomy with a poorly developed fissure, requiring a similar type of dissection. The primary disease in all these patients was tuberculosis. The only one of the 5 in whom the initial dissection was difficult was a patient (Case 10) who had had the posterior subsegment of the left apicoposterior segment resected, together with an adjacent subsegment of the anterior segment. Because of a large persistent air leak, secondary thoracotomy was performed 6 days after the original operation. An indurated area bordering the previous resection plane was removed and microscopically proved to be a typical pulmonary infarction with thrombi in the adjacent vessels. The chest tubes were removed after 2 days but, because of an enlarging apical space, a 3-rib thoracoplasty with tertiary thoracotomy was subsequently performed 3½ months later. Several small air leaks near some cotton sutures were observed. The leaks were oversewn with catgut and the space dusted with talcum powder. The patient's subsequent course was uneventful.

TABLE III. PATIENTS REQUIRING SUBSEQUENT THORACOTOMY FOR AIR LEAKS

CASE	DISEASE	INITIAL THOROCATOMY	REASON FOR SECONDARY THORACOTOMY	FINDINGS AT SECONDARY THORACOTOMY	IMMEDIATE COMPLICATIONS OF SECONDARY THORACOTOMY	LATE COMPLICATIONS
Air Leaks in Presence of Viable Tissue						
6. White male, age 32	4.5 cm. coccidioidal cavity	RU lobectomy, 9/27/55	Persistent air leak	2 mm. interlobar bronchus leaking on middle lobe surface, 10/4/55	None	None
7. White male, age 36	Fibrocaseous tuberculosis	Left apical posterior segmentectomy, 12/2/57	Persistent air leak and fever	Several small air leaks in previous resection plane; tissue viable, 12/13/57	None	None
8. White male, age 65	Epidermoid cancer, 3 cm. in diameter	LU lobectomy, 7/1/58	Persistent air leak	Two suture hole leaks on bronchial stump under pleural flap	None	Continued air leak but final spontaneous closure
9. White male, age 33	Cavitary tuberculosis	LU lobectomy and superior subsegmentectomy, 7/2/57	Persistent air leak	2 mm. bronchial leak on surface of superior segment, 7/18/57	None	None
Air Leaks in Presence of Infarcted Tissue						
10. Oriental male, age 24	Fibrocaseous tuberculosis	Multiple subsegmentectomies, LUL, 7/12/56	Persistent air leak	Infarcted subsegment containing air leaks, 7/18/56	None	Increasing apical space necessitating tertiary thoracotomy with suture of air leaks, poudrage, and 3-rib thoracoplasty, 10/31/56; good result
11. White male, age 27	Fibrocaseous tuberculosis	RL lobectomy, 10/1/58	Persistent air leak	Infarcted subsegment containing air leaks, 10/15/58	None	None
12. White male, age 26	Fibronodular tuberculosis; previous contralateral segmentectomy	R. apical and posterior segmentectomies, 12/2/58	Persistent air leak	Infarcted subsegment containing air leaks, 12/9/58	None	None
13. White male	Fibrocaseous	RU lobectomy	Persistent air	Infarcted subsegment	Massive atelec-	None

13. White male, age 45	Fibrocaseous tuberculosis	RU lobectomy, 11/14/56	Persistent air leak	Infarcted subsegment containing air leaks, 11/19/56	Massive atelectasis, pneumonia, requiring tracheostomy	None
14. White male, age 31	Cavitary tuberculosis	LU lobectomy, 4/4/57	Persistent air leak	Infarcted subsegment containing air leaks, 4/15/57	None	Bronchopleural fistula with persistent air space
			Air Leaks Attributable to Underlying Disease			
15. White male, age 43	Residual tuberculosis cavity with positive sputum	Rt. apical and posterior segmentectomy, 4/17/56	Persistent air leak	Infarcted subsegment with active tuberculosis leaking air, 4/25/56	Chest wall dehiscence	Failure of air leakage to stop; empyema; death from bronchopneumonia, 6/27/56
16. Negro male, age 30	Cavitary tuberculosis with positive sputum	Rt. superior segmentectomy, 11/17/55	Persistent air leak	Several small air leaks in intersegmental plane, 11/29/55	None	Empyema requiring drainage and 5-rib thoracoplasty 1/23/56; recovered
17. White male, age 31	Recurrent spontaneous pneumothoraces due to emphysematous blebs	Rt. apical segmentectomy and poudrage, 3/26/56	Continuing air leak	Multiple air leaks on intersegmental surface, 4/3/56; lobectomy completed	None	None
18. Negro male, age 42	Cavitary tuberculosis with destroyed rt. lung and positive sputum	Rt. pneumonectomy, 4/19/56	Bronchopleural fistula	Air leak at bronchial stump, 4/27/56	Failure to close bronchopleural fistula	Developed empyema; drained 5/15/56; eventual death from tuberculous pericarditis and right heart failure, 3/31/57
			Miscellaneous Air Leaks			
19. White male, age 38	Cavitary tuberculosis	RU lobectomy and segmentectomy, superior segment, 10/8/59	Persistent air leak	Air leak on surface of subsegment; bits of tissue resected showed microscopic squamous cell carcinoma, 10/16/59	None	Superior segmentectomy completed 11/9/59; further localized carcinoma found; uneventful recovery
20. White male, age 43	Cavitary tuberculosis	RU lobectomy, 10/22/59	2 large pneumothorax spaces with atelectasis of middle lobe	Loculated pneumothorax; atelectatic middle lobe; adherent lower lobe, 10/27/59	None	None

Small infarcted subsegments of lung parenchyma from which air was leaking were found adjacent to the original resection planes in Cases 11, 12, 13, and 14. Two of these patients (Cases 11 and 12) made uneventful recoveries following removal of indurated subsegments containing air leaks which microscopically proved to be infarcted lung tissue. The secondary thoracotomies were performed 14 days and 7 days after a right lower lobectomy and a right apical and posterior segmental resection, respectively. The remaining 2 cases in this group developed further complications. In Case 13, roentgenographic evidence of an increasing air space after a right upper lobectomy necessitated a secondary thoracotomy 5 days after the initial procedure. An infarcted superior subsegment was removed and a tailoring thoracoplasty performed. Air leakage ceased within 48 hours, but the patient developed massive atelectasis and pneumonia before eventual recovery. At secondary thoracotomy in Case 14, 11 days after a left upper lobectomy, an infarcted subsegment, leaking air on the superior surface of the lower lobe, was resected and a phreniclasia was performed. An apical air space persisted despite thoracentesis. The patient left the hospital against medical advice 6 weeks after the secondary thoracotomy. The space is still present, and the patient's sputum is positive for tubercle bacilli. Despite the presence of empyema with bronchopleural fistula, the patient refuses further surgery.

We have been unable to distinguish, preoperatively, between the air leaks from viable tissue and those arising from infarcted subsegments of lung. The temperature curves of the patients have given us no clue, and the characteristic roentgenographic appearance of subsegmental infarcts described by Salyer and Harrison was not obvious in our cases.

Persistent air leaks, even after secondary thoracotomy, were present in Cases 10 and 14, despite resection of small infarcted subsegments. Why small peripheral air leaks should have continued in these cases, as they did in the patients in the first group, remains unexplained.

A third group of patients having persistent air leaks in the immediate postoperative period is composed of those in whom this complication is attributable more to the underlying disease than to the operative procedure. In one of these, Case 15, a right apicoposterior segmental resection had been performed 5 days before for a residual tuberculous cavity with persistently positive sputum. An infarcted subsegment adjacent to the resection plane was noted to be leaking air at the secondary thoracotomy. In addition to the infarct, caseous tubercles showing acid-fast organisms were seen microscopically in the resected specimen. Even though the grossly infarcted area was removed, the air leak continued. A tuberculous empyema developed, and, after a wound dehiscence and bronchopneumonia, the patient eventually died.

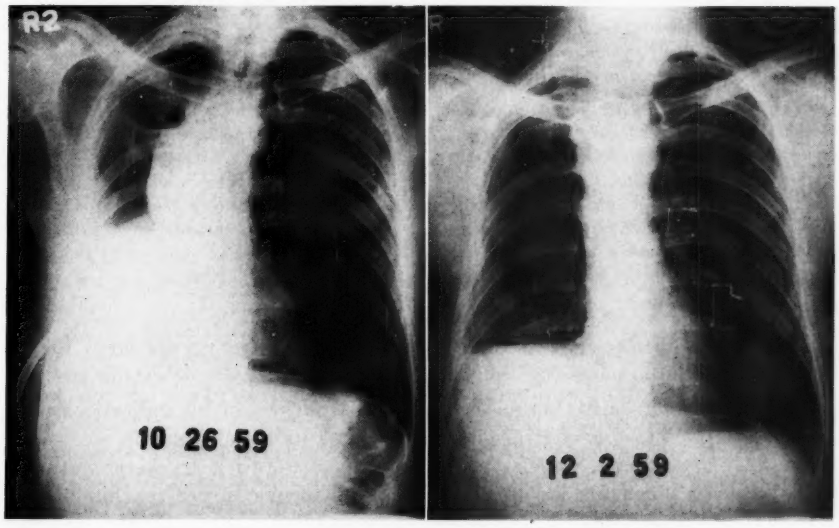
A superior segmentectomy was performed initially in Case 16, a patient who likewise had cavitary tuberculosis with persistently positive sputum. At re-exploration 12 days later, a thin film of fibrin covered the surface of the lung along the previous plane of resection. The lung appeared viable, but multiple air leaks were present. Despite suturing of these and a small tailoring thoracoplasty, the fistulas failed to close. An empyema developed which was later drained, and a more extensive thoracoplasty performed. He eventually recovered.

In Case 15, a segmental resection was performed initially instead of a lobectomy because of a markedly diminished respiratory reserve. In Case 16 segmentectomy was performed as an alternative to lobectomy, or even pneumonectomy, for cavitary tuberculosis. In retrospect, we believe that lobectomies should have been performed in both these cases because of the presence of cavitary lesions with positive sputa.[3]

A more extensive resection in Case 17 might have saved this patient a second thoracotomy. This 31-year-old man had had two spontaneous pneumothoraces in 1 month and, after the second, the lung failed to expand despite catheter drainage. At exploration, the site of the air leak was identified in the apical segment. This was resected and poudrage of the pleural space performed. Eight days later, the remainder of the right upper lobe was removed because of persistent leakage from the intersegmental surface.

The second surgical specimen showed multiple areas of emphysema in the anterior and posterior segments, with blebs measuring up to 1.5 cm. in diameter. His subsequent course was uneventful.

In Case 18, a pneumonectomy for chronic cavitary tuberculosis with a destroyed lung and persistently positive sputum had been performed. Tubercle bacilli from this patient were completely resistant to antituberculosis drugs. He developed a bronchopleural fistula with subcutaneous emphysema. At secondary thoracotomy, 8 days postoperatively, the pleural cavity contained large blood clots and multiloculated fluid. The bronchus was found to be leaking and was resutured. A culture taken of the pleural fluid yielded tubercle bacilli.



A. *B.*

Fig. 4.—Case 20. *A*, Two large pneumothorax spaces with mesial opacity in right hemithorax 4 days after upper lobectomy. Failure of lung to expand on catheter drainage. *B*, Complete re-expansion of right lower and middle lobes after secondary thoracotomy. (Phrenic paralysis produced at initial operation.)

After the second operation, the patient's pleural cavity was slow to refill with fluid, the temperature remained elevated, and thoracenteses revealed a *Staphylococcus aureus* empyema. An open drainage was performed for the mixed infected tuberculous empyema. Eleven months later, the patient died from tuberculous pericarditis, with right heart failure. At autopsy, the bronchial stump leading to the tuberculous empyema cavity was widely patent.

In all 4 patients of this last group of cases, persistent air leakage noted at re-exploration was due primarily to the disease of the patient which had been the indication for the original surgery. Cases 15, 16, and 17 had disease in the intersegmental plane; the first 2 patients having active tuberculous endobronchitis, and the third emphysematous blebs. The desirability of performing at least a lobectomy in such cases has been mentioned previously. In Case 18, a tuberculous infection of the pleural cavity, plus a debilitated patient whose power of healing was markedly reduced, combined to result in the breakdown of the bronchial stump.

The final 2 patients having secondary thoracotomies for air leaks presented individual problems.

Case 19 had had a right upper lobectomy with the additional resection of a subsegment of the superior segment of the right lower lobe for cavitary tuberculosis. Because of a

persistent air leak, a secondary thoracotomy was performed on the seventh postoperative day. The leak was found on the raw surface of the remainder of the superior segment. The tissue in the vicinity of the leak appeared viable, with the possible exception of several small tags of indurated lung tissue, not over a few millimeters in diameter. These were removed with a hemostat. The leak was not sutured because of its proximity to the superior segmental artery. The remaining lung was freed from the chest wall. Although this procedure was effective in sealing the lung leak, much to our surprise, the tags of tissue resected at the time of the secondary thoracotomy showed a microscopic area of infiltrating squamous cell carcinoma. Because of this finding, a tertiary thoracotomy was performed, with resection of the remainder of the superior segment and a partial concomitant thoracoplasty. The only abnormality noted at this operation was a small indurated area at the site of the previous lung leak. A section through this area showed another small area of infiltrating squamous cell carcinoma. Multiple microscopic sections through the remainder of the superior segment failed to reveal further tumor tissue.

Case 20, although grouped with patients having lung leaks, did not have an active leak at the time of the secondary thoracotomy. An apical air space had been present following removal of the drainage tubes after an upper lobectomy. Following a thoracentesis, another air space developed (Fig. 4, *A*). Because of failure to evacuate these spaces with catheter drainage, a secondary thoracotomy was performed. The middle lobe was found to be atelectatic and to form a partition between the two air spaces. A lysis of adhesions was performed with satisfactory expansion of the lung (Fig. 4, *B*).

DISCUSSION

In analyzing this series of secondary (and even occasional tertiary) thoracotomies, the indications for re-exploration fall into three major groups.

Massive hemorrhage with shock is the most obvious of all indications, but it is of interest that this clinical picture presented itself only once in our series (Case 3). Our other 2 patients with hemorrhage were not in shock, but had required several transfusions during the night following surgery. This history and the roentgenographic appearance of the hemithorax (Figs. 1 and 2, *A*) the following day were the decisive reasons for re-exploration, and, in a tertiary thoracotomy (Case 2), the roentgenogram alone provided the indication (Fig. 2, *B*). Despite the clinical evidence of shock in Case 3, only inconspicuous bleeding points were found at secondary thoracotomy, just as in the other 2 cases. Even if the bleeding were to stop completely, it is our belief that any appreciable amount of blood left in the thorax, as seen roentgenographically, should be manually evacuated.

Sepsis may be an indication for secondary thoracotomy. Usually the presence of infection can be diagnosed by thoracenteses and treated by drainage. If, however, no source for a patient's high fever and leukocytosis can be determined by thoracenteses, we do not hesitate to reopen the chest to find the infection, which is usually loculated.

Persistent air leak was the predominating reason for re-exploration in our series. At secondary thoracotomy, we have found three distinct underlying causes for air leakage, although the clinical pictures immediately preceding the surgery have usually been indistinguishable. Frequently the leaks have been small, usually peripheral, and the remaining lung tissue has appeared healthy. The release of adhesions about the remaining lung and the simple suture of tiny

bronchi have usually been adequate to stop the escape of air. The removal of infarcted subsegments of lung, leaking air along the resection planes, has been effective in stopping leaks in other patients. Besides being recognizable at surgery as the obvious source of leakage, these infarcted subsegments have a characteristic dark red color and are indurated on palpation. There has been no difficulty in finding the plane between the pathologic and normal tissue.

Occasionally, disease remaining in the hemithorax, either in the dissected segmental plane or, as in Case 18, in the pleural cavity itself, has been responsible for the complication. The suturing of obvious leaks or removal of small additional subsegments has not met with any marked success in this group. But, regardless of the underlying etiology of the air leak, it has been our practice generally to perform a secondary thoracotomy within a week or 10 days of the initial thoracotomy. A persistent air space and the prolonged presence of a tube in the chest increase the risk of empyema.

The results of our secondary thoracotomies have, for the most part, been gratifying. However, two tertiary thoracotomies, one for recurrent hemothorax (Case 2) and one for air leak (Case 10) have been performed, and an additional surgical procedure is indicated in Case 14. In another patient (Case 8), an air leak also persisted following re-exploration, although it finally sealed spontaneously.

Except for the patient who required further resection of an emphysematous upper lobe (Case 17), we have had our poorest results in patients in whom the leaks were caused by their initial underlying disease. Initial lobectomy rather than segmental resection in the face of sputum positive for *Mycobacterium tuberculosis* might have prevented the complications in 2 patients (Cases 15 and 16). Secondary thoracotomy was likewise ineffective in Case 18, a patient who developed a tuberculous empyema cavity and bronchopleural fistula following pneumonectomy.

In general, however, secondary thoracotomy has been a procedure which takes little time, is frequently lifesaving, and often markedly shortens convalescence and averts serious complications. In our hands, there has been no great risk in the operation. Though there were two deaths in our series, neither can be attributed directly to the secondary thoracotomy. However, the stress of surgery is certainly not to be overlooked, as in Case 13 in which atelectasis and pneumonia followed the secondary procedure. In our experience the risk is far outweighed by the beneficial effects of a satisfactory exploration. Infection of the pleural space did not result from any of the secondary thoracotomies. In Case 15, the patient's wound dehisced in the presence of tuberculous empyema, but there was no known extrinsic contamination.

Except in the patients with tuberculosis and persistently positive sputum, the complications of surgery preceding secondary thoracotomy are not peculiar to any particular pulmonary disease. The infarcted subsegments of lung responsible for air leakage were noted only in tuberculous cases, but in only 1 of these (Case 10) was the initial dissection particularly difficult. It seems most likely that similar infarcts due to a compromised circulation would be found in other diseases in a larger series of cases.

No specific type of resection appears immune to the postoperative complications leading to secondary thoracotomy. Pneumonectomy, lobectomy, and segmentectomy are all represented in our series, and all, except for the impossibility of infarcted subsegments in pneumonectomy, can be potentially complicated by air leak, bleeding, or sepsis.

Regardless of which of these three types of complications may be present, our experience indicates that, in their presence, early secondary thoracotomy should be performed, regardless of how unpleasant the prospect of such a procedure may be to the patient or to the surgeon.

SUMMARY

In the treatment of complications in a series of 356 pulmonary resections, 20 secondary thoracotomies were performed within a few hours to 3 weeks after the initial operation. The indications for re-exploration were massive hemorrhage (3 patients), sepsis (2 patients), and persistent air leak (15 patients). Results of secondary thoracotomy in individual cases are presented and discussed.

REFERENCES

1. Kent, E. M.: Conservative Management of Empyema Following Total Pneumonectomy, J. THORACIC SURG. **20**: 374, 1950.
2. Salyer, J. M., and Harrison, H. N.: Pulmonary Infarction Complicating Segmental Resection, J. THORACIC SURG. **36**: 818, 1958.
3. Steele, J. D., and Wayne, L.: The Risk of Pulmonary Resection in Tuberculosis Correlated With the Status of Preoperative Sputum, Tr. 17th Conference on the Chemotherapy of Tuberculosis, Veterans Administration-Armed Forces, 1958, p. 210.

PULMONARY RESECTION: EFFECT OF INITIAL VEIN LIGATION UPON SEQUESTRATION OF BLOOD IN THE LUNG

James T. Croley, M.D., and James D. Hardy, M.D.,***
Jackson, Miss.

INTRODUCTION

THERE are two particular reasons why it might be desirable to divide the vein prior to ligation of the artery in performing a pulmonary resection. First, in right upper lobectomy the arterial supply is often partially obscured by branches of the superior vein. In certain patients lobectomy would be much facilitated by initial division of these branches. Second, in the presence of a malignant tumor, venous cell embolization would be diminished by initial vein ligation, prior to manipulation of the lung.

Unable to find specific data in the literature with regard to the volume of blood trapped in the lung by initial vein ligation, we have investigated this problem.

METHODS AND PROCEDURE

Right upper pulmonary lobectomy was performed in 30 dogs of comparable size using light pentobarbital anesthesia and artificial pulmonary ventilation which was achieved by means of a mechanical respirator and endotracheal tube. In Group I (10 animals) initial venous ligation, in Group II (10 animals) initial arterial ligation, and in Group III simultaneous arterial and venous occlusion was effected. Following 30 minutes of venous or arterial ligation in Groups I and II (respectively) and 30 minutes of anesthesia only in Group III, the entire right pulmonary hilum was abruptly cross-clamped and divided in each dog, and the weights of the right lung in the 3 groups were compared.

RESULTS

The cumulative data are shown in Table I and are presented graphically in Fig. 1. The average weight of the right lung in Group I, in which the veins to the right upper lobe had been clamped 30 minutes prior to occlusion

From the Department of Surgery and University Hospital, University of Mississippi Medical Center, Jackson, Miss.

Supported by Army Contract DA-49-007-MD-627.

Received for publication Jan. 12, 1960.

*Assistant Resident in Surgery.

**Professor and Chairman, Department of Surgery, University of Mississippi Medical Center, Jackson, Miss.

of the arteries to this lobe, was 139.2 grams. In Group II, in which the arteries had been clamped 30 minutes prior to clamping of the veins and cross-clamping of the base of the lung, the average weight of the right lung was 108.1 grams. In Group III, in which the lung base had been abruptly cross-clamped following 30 minutes of anesthesia, occluding both artery and vein simultaneously, the average weight of the right lung was 125.5 grams. It may be seen, therefore, that an average of 31 grams of blood was apparently trapped in the lung by ligation of the veins to the right upper lobe 30 minutes prior to ligation of the arterial supply. This difference between Group I and Group II was statistically significant.

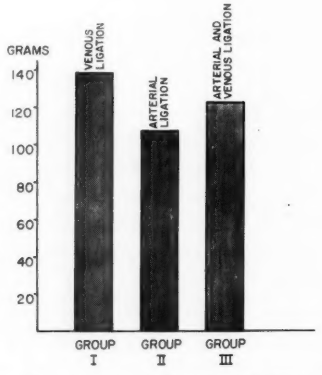


Fig. 1.—Comparison of average weights of right lungs in lobectomized dogs.

TABLE I

NUMBER OF DOG	GROUP I		GROUP II		GROUP III	
	WT. OF DOG (KG.)	WT. OF RT. LUNG (GM.)	WT. OF DOG (KG.)	WT. OF RT. LUNG (GM.)	WT. OF DOG (KG.)	WT. OF RT. LUNG (GM.)
Dog 1	13.6	130	13.6	136	13.9	95
Dog 2	15.4	120	15.4	118	15.4	110.5
Dog 3	13.6	107.5	13.6	116	14.5	145.5
Dog 4	15.4	143	15.0	106	15.7	113
Dog 5	16.4	144.5	16.4	89.2	16.4	105
Dog 6	14.1	121	14.5	87.5	14.8	123.5
Dog 7	15.9	181	14.7	87.7	16.4	112
Dog 8	13.6	127	14.5	106.5	16.8	135
Dog 9	16.4	190	14.5	113	17.3	105
Dog 10	13.6	128	14.5	120.5	17.3	190
Average weights for each group	14.80 Kg.	139.20 Gm.	14.67 Kg.	108.10 Gm.	15.84 Kg.	123.45 Gm.

DISCUSSION

These data obtained in a study of dogs are not strictly transferrable to possible alterations in man. However, on a weight basis, which is one of the indices used for estimating normal blood volumes, it would appear that initial ligation of the venous supply to the right upper lobe in a man weighing 75

kilograms might result in the sequestration of perhaps 150 c.c. of blood over a period of 30 minutes. Such a volume of blood loss would appear to be justifiable, first, to reduce technical hazards when indicated and, second, as a prophylaxis against cancer cell dissemination. It should be borne in mind, nevertheless, that a lobe or lung in which considerable amounts of blood have been sequestrated becomes more cumbersome to maneuver, and subsequent exposure of the organ for purposes of hilar dissection may become more difficult.

SUMMARY AND CONCLUSIONS

1. The volume of blood sequestrated in the right upper lobe, when the venous supply is ligated 30 minutes prior to the arterial supply, has been examined in 30 dogs. Under these circumstances, the average increase in weight of the right lung, as compared to the weight of the right lung when the artery was ligated 30 minutes prior to the vein, was 38 grams. This was considered to represent, essentially, sequestrated blood. The difference was statistically significant.

2. It is concluded that initial ligation of the venous supply to the right upper lobe in a man weighing 75 kilograms might result in the sequestration of perhaps 150 c.c. of blood over a period of 30 minutes. This volume of blood loss would appear to be justifiable in minimizing technical hazards, when indicated, and as a prophylaxis against cancer cell dissemination, when applicable.

AIR EMBOLISM FOLLOWING TRANSDIAPHRAGMATIC PNEUMOPERITONEUM

George A. Higgins, M.D., Kansas City, Kans., and*
*Theodore L. Batchelder, M.D.,** Kansas City, Mo.*

DURING recent years the use of pneumoperitoneum as a space-filling aid following pulmonary resection has been practiced in selected cases in various chest centers. In some instances, the pneumoperitoneum has been induced, as well as maintained, by the usual abdominal route. However, in other cases the pneumoperitoneum is induced transdiaphragmatically at the conclusion of operation and prior to closure of the chest.[5, 10, 11, 13, 14] It is not our purpose to discuss the possible advantages or disadvantages of the procedure, but rather to point out a serious hazard of producing pneumoperitoneum by the transdiaphragmatic route, as illustrated by the following 2 cases.

CASE REPORTS

CASE 1.—C. E. D. (KCVAH No. 30 011), a 56-year-old white man, had a 6-year history of tuberculosis. He had been treated intermittently in the hospital with drug therapy, and had fibrocavitary disease localized in the right upper lobe. The sputum was positive for acid-fast bacilli. On July 16, 1957, a right upper lobectomy was carried out.

Description of Operation.—Using endotracheal anesthesia and with the patient on his left side, a right posterolateral thoracotomy incision was made through the bed of the fifth rib, which was excised subperiosteally. The right upper lobe was contracted and fibrotic, and there were dense adhesions between the visceral and parietal pleura in this region. Right upper lobectomy was carried out with moderate difficulty. Upon re-expansion of the remainder of the lung, a small residual space remained and it was decided to induce pneumoperitoneum by means of transdiaphragmatic injection of air. An 18 gauge needle, attached to a 100 c.c. syringe by a link of rubber tubing, was used for the procedure. Attachment of the needle by means of tubing was done to prevent a change of position of the needle during injection of the air. The needle was inserted through the tendinous portion of the diaphragm, and aspiration was attempted to ensure that it had not entered a blood vessel. After injection of approximately 50 ml. of air, a typical "mill-wheel" murmur could be heard, and the blood pressure dropped to approximately 50 mm. Hg, systolic. The pericardium was quickly opened, and frothy blood could be seen in the right atrium. A needle was inserted into the atrium and the frothy blood was aspirated. A few remaining air bubbles escaped from the atrium through the needle hole following removal of the needle. The blood pressure and color of the patient quickly returned to normal. It did not appear that any of the air entered the right ventricle, and no air bubbles could be detected in the pulmonary arterial tree. No

From the Department of Surgery, University of Kansas School of Medicine, Kansas City, Kans., and the Veterans Administration Hospital, Kansas City, Mo.
Received for publication Jan. 11, 1960.
*Present address: Mt. Alto Veterans Administration Hospital, Washington, D. C.
**Present address: Jacksonville, Fla.

further attempt to induce pneumoperitoneum was made and the incision was closed in the usual manner. The postoperative course was entirely uneventful, and there were no signs of residual damage from possible hypoxia or air embolism. The patient made an uneventful recovery, and has since been discharged from the hospital.

CASE 2.—K. U. M. C. (No. 59-1494), a 38-year-old white man, had a history of pulmonary tuberculosis of 8 years' duration, marked by numerous discharges from the hospitals against medical advice and failure to remain on drug therapy. Surgical extirpation of well-localized disease in the right upper lobe had been recommended to him on two prior occasions, which he refused. The sputum was positive for acid-fast bacilli. The chest roentgenograms showed bilateral apical fibrosis with a large cavity in the right upper lobe.

Description of Operation.—Preliminary bronchoscopy was done under general anesthesia which revealed cephalad rotation of both upper lobe bronchi with no evidence of stenosis or endo-bronchial tuberculosis. The endotracheal tube was then inserted and the patient was placed in a full lateral position with the right side upward. A posterolateral incision was utilized, resecting the fifth rib subperiosteally. The pleural space was completely obliterated by avascular filmy adhesions on all surfaces. Extrapleural dissection was necessary over the posterior segment of the upper lobe, which contained the cavity. Upper lobectomy was accomplished without difficulty. Adhesions over the middle and lower lobes were then divided so as to allow the lobes to shift upward. With the lobes inflated, a residual space was present to the level of the upper border of the fourth rib posteriorly. Pneumoperitoneum was then attempted, using a 50 c.c. syringe, a 3-way stopcock, and an 18 gauge needle. The tendinous portion of the diaphragm was grasped with two Allis clamps and tented upward. This was done in order to separate the diaphragm from the underlying liver, and thus create a slight vacuum in the subphrenic space. The diaphragm did not seem to separate well from the liver although it did tent upward with traction. The plunger of the syringe was lubricated with saline solution so as to slide freely and was set at the 25 c.c. mark. The stopcock was set with the syringe channel open to the needle, which was then passed through the tented diaphragm. A negative pressure was not detected, as indicated by failure of the plunger to move inward of its own accord. The needle was re-situated several times, until it was thought to be in free subphrenic space. No blood could be withdrawn at this point and approximately 100 c.c. of air was injected. Attempts to withdraw air as it was being injected in small lots were not successful, and it was decided not to inject more air. At this point a "washing-machine sound" was clearly audible, which was synchonous with the heartbeat. The lung was immediately retracted posteriorly, the pericardium grasped with Allis clamps, and a 1 cm. incision was made with scissors which included the underlying atrial wall. A foamy mixture of air and blood spurted forth, which was allowed to continue until only blood flowed. Bleeding was then controlled with a finger tip and the pericardial incision was extended parallel to the phrenic nerve. Remaining air was then visible entrapped in the atrial appendage. By depressing the appendage and making the small atriotomy the highest point, the air readily escaped. Total loss of blood from the atriotomy was 300 to 400 ml. The systolic blood pressure dropped from 110 mm. Hg to 50 mm. Hg at the time air embolus was first recognized, and gradually returned to normal after the foam was released. The atriotomy was closed with a continuous suture of 4-0 silk, and the pericardial edges were re-approximated with interrupted sutures. The incision was then closed in layers. The patient responded to vocal stimuli within 15 minutes after completion of the operation, and had a rapid and uneventful convalescence. No evidence of central or peripheral nervous system deficit could be detected.

DISCUSSION

Air embolism and the physiologic alterations produced by air in the vascular system have been well studied and recorded. One of the most extensive studies was published by Senn[12] in 1885 following numerous experiments using cats, dogs, sheep, horses, and pigs. He cites prior studies by Virchow, Panum, and

others. These, as well as more recent reports, indicate that air introduced into the systemic venous system becomes trapped in the right heart and in the pulmonary arterial bed with a resultant blockage of blood flow. The amount of air necessary to produce death apparently differs from species to species as well as in different animals of the same species. Oppenheimer and associates[9] report that the amount of air required to kill dogs varies from 5 to 75 ml. per kilogram body weight, and that the animals tolerate more air when lying on the left side. Wolffe and Robertson[15] found that in the dog an average of 15 ml. of air per kilogram body weight were required to produce death, while in the rabbit only 0.5 ml. per kilogram was fatal. The lethal dose of intravenous air in man is, of course, unknown.

Air introduced into the systemic venous system remains trapped in the heart and pulmonary artery tree and does not enter the left heart or systemic arterial bed unless a right-to-left shunt is present. That air does not readily enter the left heart is a fortunate circumstance, since bubbles passing through the left side quickly cause death by obstruction of the coronary arteries. Air emboli to the cerebral circulation may also lead to permanent central nervous system defects.

Constant awareness of the possibility of air embolization and early recognition of its existence are of prime importance in prevention of death. Based on animal studies,[3, 7] as well as recorded experiences following air embolization in man, it has been recommended that the individual be placed on his left side, thus, permitting the air to be pumped out of the right heart and into the right (uppermost) pulmonary arterial bed. This permits effective function of the right heart, oxygen exchange in the left lung, and gradual absorption of the bubbles entrapped in the right lung. There is some indication that the Trendelenburg position may also be useful.[1] Several authors[4, 6, 8] have cited the results of experiments on the dog which suggest that aspiration of the right ventricle should be done when air embolization occurs. The literature contains at least one record of attempted aspiration of the right ventricle in man.[8]

Although there are numerous avenues by which air may enter the systemic venous system with resultant air embolism, we are primarily concerned with its occurrence during induction or refill of pneumoperitoneum. Burman[2] has reviewed the published cases rather carefully and suggests an incidence of 1 in 437 pneumoperitoneums. Of particular interest in his report is the suggestion that several cases were due to the introduction of air into the liver. To pursue this concept further, as it might pertain to our experiences just recorded, the following study was carried out: A dog, weighing 10 kilograms, was placed on its left side under general endotracheal anesthesia, with controlled respirations. The right chest was opened through the seventh intercostal space. A small opening was made through the dome of the right diaphragm, and 30 ml. of air was injected into the substance of the liver by means of a syringe and needle. Immediately thereafter, air bubbles were visible in the inferior vena cava, in the right atrium, and pulmonary artery branches to the right lung. This was accompanied by a typical "mill-wheel" murmur. The air passed readily into the right ventricle and pulmonary tree in the dog, and did not seem to accumulate in the atrium, as it had in the two clinical cases observed in man. This

suggests that the relationships and position of the chambers of the dog's heart may be such that the dog is not an entirely suitable animal for the study of the mechanism of death in air embolism as it pertains to man. However, it could clearly be demonstrated that air injected into the parenchyma of the liver quickly appeared as bubbles in the inferior vena cava.

This observation leads to the conclusion that in the cases herein reported, air was inadvertently injected into the liver with resulting air embolism. The mechanism for this occurrence in Case 2 is explained by the presence of adhesions between the diaphragm and the liver. As the diaphragm was drawn upward with the Allis clamps, small rents in the capsule of the liver were probably produced, through which air under pressure dissected its way into the hepatic parenchyma. It is suggested that if transdiaphragmatic pneumoperitoneum is to be induced, a small incision should be made in the diaphragm through which a catheter may be passed into the free peritoneal space for introduction of the air. In the presence of adhesions between the liver and diaphragm, transdiaphragmatic pneumoperitoneum would be contraindicated.

SUMMARY

Two cases of air embolism occurring at the time of transdiaphragmatic pneumoperitoneum are reported, both cases following right upper lobectomy. Both patients recovered uneventfully following removal of the air from the right atrium. Animal studies showed that air injected into the substance of the liver found its way immediately into the inferior vena cava and right heart, suggesting the pathway of the air in the 2 cases reported.

Use of a catheter passed through a small incision in the diaphragm is suggested to prevent introduction of air into the liver and resulting air embolization. Adhesions between the liver and diaphragm should be considered contraindication to transdiaphragmatic pneumoperitoneum.

REFERENCES

1. Bohorfoush, J. C.: Air Embolism, Am. Rev. Tubere. **47**: 263, 1943.
2. Burman, D.: Air Embolism During Pneumoperitoneum Treatment, Thorax **11**: 49, 1956.
3. Forbes, G.: Air Embolism as a Complication of Vaginal Douching in Pregnancy, Brit. M. J. **2**: 529, 1944.
4. Joffe, H. H., and Wells, A. H.: Air Embolism, Minnesota Med. **29**: 1238, 1946.
5. Kinsella, T. J.: Personal communication.
6. Larson, C. P.: Venous Air Embolism, Am. J. Clin. Path. **21**: 247, 1951.
7. Moore, R. M., and Braselton, C. W., Jr.: Injections of Air and of Carbon Dioxide Into a Pulmonary Vein, Ann. Surg. **112**: 212, 1940.
8. Musgrove, J. E., and MacQuigg, R. E.: Successful Treatment of Air Embolism, Clinical Notes, J. A. M. A. **150**: 28, 1952.
9. Oppenheimer, M. J., Durant, T. M., and Lynch, P.: Body Position in Relation to Venous Air Embolism and the Associated Cardiovascular-Respiratory Changes, A. J. Med. Sc. **225**: 362, 1953.
10. Paul, J. S.: Personal communication.
11. Salyer, J. M.: Personal communication.
12. Senn, N.: An Experimental and Clinical Study of Air-Embolism, Transactions of the American Surgical Association **3**: 197, 1885.
13. Strieder, J. W.: Personal communication.
14. Ware, P. F.: Personal communication.
15. Wolffe, J. B., and Robertson, H. F.: Experimental Air Embolism, Ann. Int. Med. **9**: 162, 1935.

DIGITALIS IN SURGERY: EXTENSION OF CLASSICAL INDICATIONS

Myron W. Wheat, Jr., M.D., Gainesville, Fla., and*
*Thomas H. Burford, M.D.,** St. Louis, Mo.*

ATRIAL FIBRILLATION, atrial flutter, and congestive heart failure are three of the most common cardiac complications following major surgery. This is particularly true in thoracic surgery when significant amounts of pulmonary tissue are resected. If not promptly diagnosed, and correctly and speedily treated, these complications may mean the difference between recovery and death in the seriously ill patient. As surgical and anesthetic techniques have improved along with advances in blood, fluid, and antibiotic therapy, the benefits of surgery have been extended to older and more critically ill patients. With this further extension of surgery, more patients are operated upon who have a cardiopulmonary system that is barely adequate even if recovery from major surgery is uneventful. Postoperatively, in the presence of atelectasis and the accumulation of endobronchial secretions, the precarious balance may be easily upset and, if atrial fibrillation, atrial flutter, congestive heart failure, or other cardiac complications arise, a vicious circle may be set up which can lead to the death of the patient. If the patients most apt to get in trouble from these arrhythmias could be selected preoperatively, they might be benefited by prophylactic digitalization, since digitalis is the drug of choice in the treatment of atrial fibrillation, atrial flutter, supraventricular tachycardia, and congestive heart failure.

Levine[1] was the first to report the postoperative occurrence of cardiac arrhythmias under the heading of "Acute Cardiac Upsets Occurring During or Following Surgical Operations." His report appeared in 1920 and concerned 9 patients, none having thoracic surgery, 3 of whom developed paroxysmal auricular tachycardia, 4 auricular fibrillation, and 2 paroxysmal auricular flutter. He suggested the use of digitalis as the treatment of choice in such instances.

Much later[2, 3, 4] reports began to appear calling attention to the significant incidence of cardiac arrhythmias following thoracic operations, and their treatment with drugs such as quinidine and atropine was suggested.[7] However,

Received for publication Jan. 4, 1960.
*Department of Surgery, University of Florida College of Medicine, Gainesville, Fla.
**Chest Service, Barnes Hospital, St. Louis 10, Mo.

there has been no conclusive evidence presented to support the use of any drug as a prophylactic measure for these arrhythmias in patients about to undergo major intrathoracic surgery.

In 1952, one of us (T. H. B.) began to use digitalis prophylactically in certain patients on the chest service at Barnes Hospital. To evaluate the results of using digitalis prophylactically, we reviewed all cases of the chest service at Barnes Hospital from 1948 to 1957 in which the patients had a major intrathoracic operation and were 55 years of age or older. There were 439 patients who fell into this group, which included 212 pneumonectomies, 138 lobectomies, 26 bilobectomies, or lobectomies and segmental resections, and 63 esophageal resections. Patients who were digitalized prior to surgery because of atrial fibrillation or congestive heart failure were not included. All 439 patients either were discharged following essentially uneventful postoperative courses, having survived at least 2 weeks following surgery, or developed a cardiac complication prior to death. These 439 patients were then divided into four groups on the basis of their ages: 55 to 59, 60 to 64, 65 to 69, 70 and over. Each of these four age groups was then divided into two subgroups A and B.

In Subgroup A were those patients who received no digitalis or, in several cases, obviously inadequate amounts of digitalis prior to surgery. In Subgroup B were those patients who received what seemed to be a reasonable amount of digitalis as a prophylactic measure either preoperatively (the majority), immediately postoperatively or, in a few, several days postoperatively, but prior to the development of any cardiac complications. Electrocardiograms were taken on all but 4 patients prior to surgery, and postoperative irregularities were verified in most instances by additional electrocardiograms.

These cases do not represent the ideal situation in which consecutive cases are alternately placed in two categories, but they are consecutive as to operations, and starting in 1952 they were digitalized in a rather random fashion. The number of cases prior to 1952 is 122 with no digitalis therapy and there was a cardiac complication rate of 24 per cent. There were 180 cases after 1952 with no digitalis used and a complication rate of 20 per cent. This difference is not significant.* Also, the great majority of the older patients in both groups occurred after 1952 when we began to use digitalis intermittently as a prophylactic measure. In the total group of 439 patients, 302 received no digitalis prior to the development of cardiac complications, and 137 patients received digitalis prophylactically. In Subgroup A, the no-digitalis group, cardiac complications developed in 68 patients (23 per cent), as compared to 16 patients (12 per cent) in Subgroup B with prophylactic digitalis.† The probability that such a large difference in the complication rates could be due to chance patient variation is about 1 in 100, on the hypothesis that the rates are the same or that digitalis has some effectiveness. In other words, it is reasonable to conclude that digitalis was effective in some degree in preventing cardiac complications.

*$\chi^2 = 0.41$; $0.50 < p > 0.70$ (two-tailed test).
†p 0.01 (one-tailed test).

As is shown in Figs. 1 and 2, patients, in the group 55 to 60 years of age, tolerated thoracic operations relatively well but, even so, cardiac complications developed at the rate of 14 per cent without prophylactic digitalis as compared to 6 per cent with prophylactic digitalis. This difference was most striking in the patients over the age of 70 of whom 46.4 per cent suffered cardiac complications if no digitalis was given; only 10 per cent suffered cardiac complications if prophylactic digitalis was given.

There were 210 pneumonectomies performed. In 55 patients, or 26 per cent, cardiac complications developed. In 119 patients having right pneumonectomies, complications developed in 29 per cent. In 91 patients with left pneumonectomies, there were cardiac complications in 22 per cent.* Seventy-five of the patients with pneumonectomies received digitalis prophylactically and complications developed in 11, or 15 per cent, as compared to 39, or 29 per cent, of 135 patients not prophylactically digitalized.

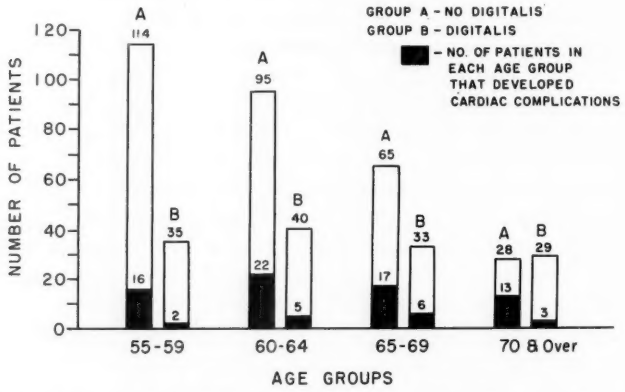


Fig. 1.—A bar graph which shows the total number of patients in each age group, divided into Subgroup A (no digitalis) and Subgroup B (prophylactic digitalis), with the number of patients developing cardiac complications in each group indicated by the shaded areas.

Cardiac complications occurred in 15 (25 per cent) of 61 patients undergoing esophagectomy. In only 1 patient of 11 receiving digitalis prophylactically were cardiac complications encountered as compared to 14 (28 per cent) of 50 patients with esophagectomy who did not receive digitalis prophylactically. There was no difference in complication rate in the two groups who underwent lobectomies. In the group of 24 patients who had bilobectomies, cardiac complications occurred in 5 (21 per cent) and all 5 were 60 years of age or over. Only 1 of these 5 received prophylactic digitalis, a patient, 61 years old with a history of asthma and dyspnea on exertion, who developed atrial fibrillation.

Anesthesia experiences were reviewed in regard to the course of the anesthesia, the anesthetist, and the premedication administered. There were no significant differences in the course of anesthesia in those patients in whom

*$0.20 < p > 0.30$ (two-tailed test).

complications occurred and those in whom complications were absent. Experienced nurse anesthetists administered the anesthesia in 362 cases, with a 20 per cent rate of cardiac complications, and doctor anesthesiologists administered the anesthesia in 73 cases, with an 18 per cent cardiac complication rate. The premedication in most instances consisted of morphine and atropine given either subcutaneously or intramuscularly.

A review of the preoperative symptoms of these patients revealed that significant pulmonary emphysema and/or true dyspnea on exertion were two of the most significant findings. There were 8 patients with moderate or severe pulmonary emphysema as revealed by x-ray studies of the chest, and 4 of these patients had complications: atrial fibrillation developed in 2, and a severe

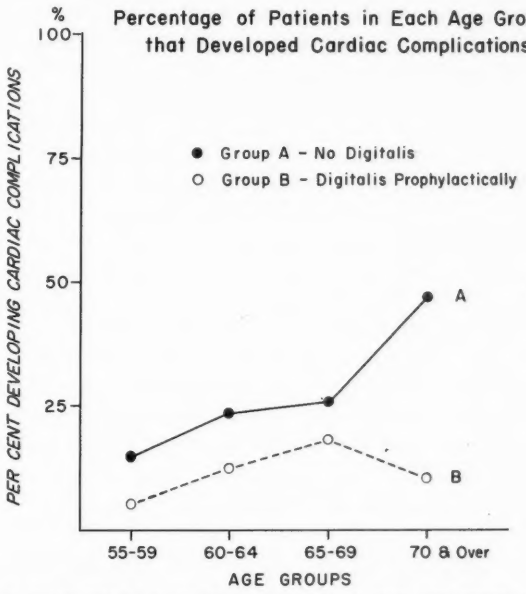


Fig. 2.—A graph which shows the percentage of each age group in which the patients developed cardiac complications—without digitalis *(top line)* and with prophylactic digitalis *(bottom line)*. (The total number of patients in each age group equals 100 per cent.)

supraventricular tachycardia in 1; the fourth patient, the only one digitalized prophylactically, died of a massive myocardial infarct. The operations performed on these 4 patients were lobectomies in 3 and a bilobectomy in 1. Electrocardiograms, as a rule, gave no additional help in predicting the development of arrhythmias unless there was an obviously significant finding, but the tracings were very important as a yardstick for comparison postoperatively. In the 202 patients with electrocardiograms which were not considered to be strictly normal, such as "border-line record," "extrasystoles," etc., the complication rate was 22 per cent or no greater than in the nondigitalized group. In those patients with histories of high blood pressure, asthma, episodes of heart failure, or a definite previous myocardial infarct, complications occurred in 29 per cent as compared to an over-all average of about 20 per cent.

A detailed analysis of the 68 nondigitalized patients in whom cardiac complications developed shows that in 47, or 69 per cent, atrial fibrillation developed as the primary difficulty, congestive heart failure occurred in 13, and supraventricular tachycardia in 5. Three became pulmonary cripples with a cardiac component difficult to assess. In 57, or 84 per cent, of these 68 patients, the complications occurred within the first 7 days following surgery, and 41 (60 per cent) of the cardiac complications occurred within the first 72 hours after surgery. Forty-eight of these 68 patients, or 71 per cent, had a very stormy postoperative course as a result of their cardiac complications, with the development of such conditions as shock, cyanosis, episodes of atrial fibrillation, and/or atrial flutter, which frequently were difficult and occasionally impossible to bring under control. In these 68 patients, pneumonectomies were performed in 39 (60 per cent), esophageal resections in 16, lobectomies in 10, and bilobectomies in 3.

In the group of patients who received prophylactic digitalis and in whom cardiac complications developed, atrial fibrillation or flutter occurred in 13 (81 per cent). However, in marked contrast to the complications in the patients without digitalis, the atrial fibrillation in 8 (50 per cent) patients with prophylactic digitalis was slow and of academic interest only, or was readily and easily converted with the use of increased digitalis and occasionally with the addition of quinidine. Of the remaining 8 patients, 3 died of massive myocardial infarctions; 3 were difficult to handle because of recurrent episodes of pulmonary edema, atrial fibrillation, respiratory insufficiency with shock, heart failure, or paroxysmal atrial tachycardia; and 1 died with uncontrolled atrial fibrillation and flutter. The operations in this group of 16 patients were pneumonectomies in 11 (69 per cent) and lobectomies in 5. There was no difference in the over-all mortality rate (5 per cent) in the groups with or without prophylactic digitalis.

DISCUSSION

The reports[2-8] relating to cardiac arrhythmias following thoracic surgery all stress the same general facts: (1) thoracic surgery in patients over the age of 60 frequently is followed by cardiac arrhythmias, 20 to 30 per cent; (2) these arrhythmias are predominantly atrial fibrillation or flutter; (3) they uniformly respond to digitalis; and (4) their greatest frequency is following pneumonectomies.

All of the articles reporting cardiac complications following thoracic surgery were searched for the possibility of compiling all the data in one report. However, only two reports[6, 8] listed their patients so that they could be fitted into our age scheme as shown in Table I.

The remaining authors[2-5, 7] do not segregate their patients in such a way that they can be fitted into this scheme but their experiences are much the same as ours. Humphreys,[5] for instance, reported an incidence of cardiac arrhythmias in patients after pneumonectomy of 32.4 per cent as compared with 5.4 per cent after lobectomy.

TABLE I*

AUTHOR	NO. OF COMPLICATIONS	NO. WHO DEVELOPED CARDIAC COMPLICATIONS	PER CENT
Under Age 60			
Krosnick and Wasserman[6]	38	1	1.2
Cohen and Pastor[8]	65	8	12.3
Over Age 60			
Krosnick and Wasserman[6]	44	9	20.0
Cohen and Pastor[8]	27	7	26.0

*This table contains data from 2 reports[6, 8] of patients segregated into those under 60 years of age and those over 60, and shows the complications to be at least twice as great in those over the age of 60.

On the basis of our findings and those of others, we believe that certain concepts should be emphasized. The withholding of digitalis until the old classical indications appear, such as auricular fibrillation with a rapid ventricular rate or congestive heart failure, is no longer justified. It is imperative in this day of modern surgery, that patients 60 years of age or over facing major surgery should be digitalized prophylactically before the development of cardiac complications in order to enhance their chances of survival. Our study shows a reduction in complication rate of 10 per cent.* Using this as an approximation to the "true rate," in our own series of 302 patients without digitalis, 30 patients could probably have been spared a cardiac complication.

We believe that the evidence now at hand is unequivocal concerning the patient over the age of 60. This problem is not generally appreciated by many internists and surgeons. With careful and intelligent use, we are convinced that digitalis as a routine prophylaxis in these selected cases does not represent a hazard. In our opinion it is a hazard not to use it. At present, we routinely digitalize all patients 60 years of age or over who are scheduled for major surgery. Under the age of 60, the patients are digitalized individually on the basis of their appearance, estimated cardiac and pulmonary status, and the magnitude of the contemplated operation. Postoperatively, the patients are maintained on digitalis as long as there seems to be an indication for it.

CONCLUSIONS

1. Intrathoracic resections in patients over the age of 60 are followed by cardiac complications in 20 to 30 per cent of these patients.

2. These cardiac complications occur most frequently following pneumonectomy (29 per cent).

3. These complications occur usually within the first week following surgery, are predominantly atrial fibrillation and/or atrial flutter, and uniformly respond to digitalis administration.

4. Cardiac complications following major intrathoracic resections can be reduced from 20 to 10 per cent in patients over the age of 55 by prophylactic preoperative digitalization.

*Ninety-five per cent confidence limits, using a normal curve approximation, show the reduction to be between 2.8 and 17.2 per cent.

5. Pulmonary emphysema and/or dyspnea on exertion when present are the two most important factors in the preoperative evaluation of patients facing thoracic surgery.

6. All patients over 60 years of age or over in whom a major intrathoracic resection is contemplated should be digitalized routinely preoperatively.

REFERENCES

1. Levine, S.: Acute Cardiac Upsets, Occurring During or Following Surgical Operations, J. A. M. A. **75**: 795-799, 1920.
2. Bailey, C. C., and Betts, R. H.: Cardiac Arrhythmias Following Pneumonectomy, New England J. Med. **229**: 356-359, 1943.
3. Currens, J. H., White, P. D., and Churchill, E. D.: Cardiac Arrhythmias Following Thoracic Surgery, New England J. Med. **229**: 360-365, 1943.
4. Massie, E., and Valle, A. R.: Cardiac Arrhythmias Complicating Total Pneumonectomy, Ann. Int. Med. **26**: 231-233, 1947.
5. Humphreys, P. C.: Cardiac Arrhythmias Following Thoracic Surgery, Bull. Moore-White Medical Foundation **2**: 46-51, 1951.
6. Krosnick, A., and Wasserman, Fred: Cardiac Arrhythmias in the Older Age Group Following Thoracic Surgery, Am. J. M. Sc. **230**: 541-550, 1955.
7. Cerney, C. I.: The Prophylaxis of Cardiac Arrhythmias Complicating Pulmonary Surgery, J. THORACIC SURG. **34**: 105-110, 1957.
8. Cohen, M. G., and Pastor, B. H.: Delayed Cardiac Arrhythmias Following Non-Cardiac Thoracic Surgery, Dis. Chest. **32**: 435-440, 1957.

DRUGS OTHER THAN STREPTOMYCIN, PARA-AMINOSALICYLIC ACID, AND ISONIAZID IN THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS

David V. Pecora, M.D., Ray Brook, N. Y.

INTRODUCTION

SINCE ORIGINAL THERAPY of pulmonary tuberculosis with streptomycin (SM), para-aminosalicylic acid (PAS), and isoniazid (INH) has proved exceedingly successful, attention is shifting to patients who have hitherto been proved incurable because they harbor drug-resistant organisms.

Nonsurgical regimens consisting of cycloserine or pyrazinamide, combined with isoniazid, have yielded excellent results.[1, 2] On the other hand viomycin with pyrazinamide,[3] cycloserine with pyrazinamide,[4] and viomycin with cycloserine[5] have not often achieved cavity closure or eliminated infectious sputum. Kanamycin plus PAS appears to be highly effective,[6] but kanamycin alone has proved discouraging.[7] Early experiences with Promizole proved disappointing,[8] and further study has been discouraged by the advent of more effective drugs. However, Lincoln and associates[9] reported good results in the treatment of miliary tuberculosis. Amithiozone appears to be as effective against the tubercle bacillus as PAS.[10] Oxytetracycline produces good clinical results only when combined with other potent drugs, such as streptomycin.[11]

Since nonsurgical therapy generally yielded such poor results, it was inevitable that surgery should be attempted. Surgery in the presence of extensive disease without effective drug therapy offered no improvement.[12] Good results have been reported following pulmonary resection performed under the protection of regimens containing pyrazinamide, viomycin, cycloserine, and Promizole[3, 13, 14] but, because the number of cases reported is not large, information is fragmentary.

MATERIALS AND METHODS

From May 1, 1954 to Aug. 1, 1959, 190 patients at the Ray Brook State Tuberculosis Hospital were subjected to regimens containing the following "secondary" drugs: amithiozone, cycloserine, kanamycin, oxytetracycline, Promizole, pyrazinamide, and viomycin. Whenever possible, these drugs were administered in combination with SM, PAS, or INH, but since most of the

From the Ray Brook State Tuberculosis Hospital, Ray Brook, N. Y.
Received for publication Jan. 25, 1960.

patients' organisms were resistant to the latter three drugs, this was not commonly possible. Except in very early cases in this series, drugs to which the patients' organisms were resistant were not continued after "secondary" drugs had been started. Drug therapy has been coordinated with surgery whenever possible and has been administered for only a few days prior to operative intervention. Combinations of two drugs have been employed in the hope of increasing effectiveness and delaying the emergence of resistance. An attempt is made to give patients, who are infectious at the time of surgery, a year of effective drug therapy. The following daily dosages usually have been prescribed: amithiozone, 150 mg.; cycloserine, 500 mg.; kanamycin, 500 mg.; oxytetracycline, 1 Gm.; Promizole, 6 Gm.; and pyrazinamide, 3 Gm. Viomycin, 1 Gm. twice a day, is given twice weekly. Indications for treatment are listed in Table I.

TABLE I. INDICATIONS FOR DRUG THERAPY

Nonsurgical		51
Surgical		218
Pulmonary resection	167	
Other surgery	51	
Miscellaneous		4
Total		273

Organisms were considered sensitive to the "secondary" drugs if the host had never received them previously. In vitro susceptibility was determined by inoculating organisms upon (Hohn's) egg medium containing 25 mcg. per milliliter of cycloserine or viomycin, 10 mcg. per milliliter of SM or PAS, or 1 mcg. per milliliter of INH. Dubos liquid medium, containing 1.25 mcg. per milliliter of kanamycin, was also used. Direct sensitivity tests to SM, PAS, and INH were read in 6 weeks. Indirect sensitivity tests to SM, PAS, and INH and all of the cycloserine and viomycin tests were read in 4 weeks. Kanamycin tests were read in 2 weeks. For the purpose of this study any growth in the presence of a drug was considered evidence of bacterial resistance to the drug, provided there was abundant growth in the control tube.

For the purpose of analysis, pulmonary resections were divided into infectious and noninfectious groups, depending upon whether or not culturable tubercle bacilli had been recovered from the tissue removed or from the expectorations at the time of surgery, since the prognosis in these two groups differs considerably. Postoperative tuberculous complications include failure of the expectorations to become noninfectious in the absence of a contralateral source of infectious sputum, empyema, and recurrence, with persistence, of infectious sputum. The mere presence of viable tubercle bacilli in the sputum for a short period of time followed by their disappearance without altered treatment is not considered a complication in this study. Early complications include those occurring within the first 6 postoperative months; late complications include the remainder.

Surgery other than resections is listed separately but, because of the multiplicity of problems involved, only certain general statements are made. The extent of disease is classified according to the standards of the National Tuberculosis Association.

RESULTS

Nonsurgical Treatment.—Fifty-one patients (42 far-advanced and 9 moderately advanced), mostly "treatment failures," were treated with various "secondary" drug regimens. All but 3 had infectious expectorations at the start of therapy. Three of the 48 infectious patients became noninfectious; and all 3 received regimens containing INH. Seventeen, or 33 per cent, are dead.

Pulmonary Resection.—One hundred and sixty-seven pulmonary resections were performed upon 147 patients. Thirty-three of the resections were performed upon 31 patients who did not harbor culturable tubercle bacilli. Twenty-two of the noninfectious patients had far-advanced, 10 moderately advanced, and 1 minimal disease. Procedures included 7 lobectomies, 10 segmental resections, and 16 wedge resections. There were no tuberculous complications. Two patients died after leaving the hospital, as a result of suicide and glomerulonephritis, respectively.

TABLE II. PULMONARY RESECTIONS IN INFECTIOUS PATIENTS*

DRUG REGIMEN	NUMBER OF PROCEDURES	EXTENT OF DISEASE			PROCEDURE				TUBERCULOUS COMPLICATIONS	
		MIN.	MOD.	F.A.	P	L	S	W	EARLY	LATE
PZA	19		6	13	2	7	5	5	5	1
VIO	1			1	1					
PZA + SM	3		1	2		1	2			
PZA + PAS	8		3	5		5	2	1		
PZA + INH	1			1		1				
PZA + VIO	24		4	20	4	12	8		3	1
PZA + PRO	4			4		2	1	1		1
PZA + AMI	1		1			1			1	
PZA + CYC	4		2	2	1	1	1	1	1	
PZA + KAN	1			1		1				
PZA+INH+VIO	1			1		1				
VIO + PAS	2		1	1	1	1			1	
VIO + INH	2		1	1		1	1			
VIO + CYC	28		9	19	1	11	8	8	3	1
CYC + SM	6		4	2		1	2	3		
CYC + INH	4		2	2		1		3		
CYC + KAN	4		1	3		3		1		
CYC + PRO	2			2			1	1	1	
PRO + SM	1		1			1			1	
PRO + KAN	15		4	11	3	5		7	1	
KAN + PAS	3		1	2				3		
Totals	134		41	93	13	56	31	34	17	4

*Legend: AMI—amithiozone; CYC—cycloserine; KAN—kanamycin; PRO—Promizole; PZA—pyrazinamide; VIO—viomycin.

MIN.—minimal, MOD.—moderate, F.A.—far-advanced.

P—pneumonectomy, L—lobectomy, or lobectomy and segment and/or wedge, S—segmental resection or segmental and wedge, W—wedge.

Table II summarizes the results of 134 pulmonary resections performed upon 116 patients who harbored culturable tubercle bacilli. Although this group contained many of the worst surgical risks with advanced disease, there was an early tuberculous complication rate of only 12.7 per cent and a total rate of 15.7 per cent. It is noteworthy that practically all of the postoperative tuberculous complications occurred early. There were 9 (7.8 per cent of the patients) deaths in this group, 5 attributable to cardiorespiratory insufficiency, 2 to hepatotoxicity, presumably due to pyrazinamide, 1 to amyloidosis, and 1 to a late

coronary occlusion. Fifteen (12.9 per cent) of the patients still have infectious sputum, and it is hoped that by additional surgery this number may be reduced. Ninety-two (79 per cent) of the patients are well and noninfectious. Seven of the latter required reoperation after the previous procedures had been unsuccessful.

Regarding the comparative efficacy of the various drug regimens listed in Table II no conclusions can be drawn, except to note, as previously,[13] that pyrazinamide alone yielded the poorest results. This is probably due to the early emergence of resistant tubercle bacilli.[15] In some instances, regimens were shifted postoperatively, usually because of drug toxicity, but occasionally when organisms thought to be resistant to SM, PAS, and INH were later found to be sensitive to one or more of these drugs. These data are not included in the table since it cannot be shown that changes in regimen affected results. It is believed that follow-up is not of sufficient duration to evaluate the importance of duration of therapy.

Two bilateral pulmonary resections performed upon patients with atypical acid-fast infections with the aid of "secondary" drugs were uncomplicated.

Other Surgery.—Table III lists 50 nonresectional surgical procedures performed with "secondary" drug therapy. Few conclusions can be drawn from this group except that, whenever surgery accomplished removal or obliteration of pulmonary cavities or pleural empyemas, the results were excellent. When these requisites were satisfied, Monaldi cavernostomy,[16] pulmonary decortication, and modified Schede thoracoplasty[17] yielded excellent results. Standard and plombage thoracoplasty have been less successful since their use has not closed many cavities in patients with advanced disease. "Secondary" drugs failed to influence the organisms in even the smallest pulmonary cavities and pleural empyemas. Indeed, in this series, failure to achieve a noninfectious state following surgery almost invariably indicated the presence of a pleural empyema or residual pulmonary cavity.

TABLE III. OTHER SURGERY PERFORMED WITH ANCILLARY DRUG THERAPY

PROCEDURES	NUMBER
Pulmonary decortication	9
Decortication + thoracoplasty	4
Thoracoplasty (standard or plombage)	17
Modified Schede thoracoplasty	6
Removal of infected plomb	2
Monaldi cavernostomy	8
Monaldi + thoracoplasty	3
Plastic repair of infected chest wall	1
Total	50

Miscellaneous.—Four patients without evidence of pulmonary cavitation or empyema, who had previously had pulmonary resection under other drug regimens, were treated with "secondary" drugs for infectious expectoration. One of these patients had a superficial infection of a bronchial stump. All 4 achieved a noninfectious state with drug therapy alone.

Toxicity.—Table IV indicates the incidence of toxicity severe enough to discontinue drugs temporarily or permanently. Manifestations are listed in Table V. It is interesting to note that toxicity to kanamycin occurred in 2 of 3 patients who received 1 Gm. a day for more than 6 months. None of 32 patients who received 0.5 Gm. of kanamycin a day developed evidence of toxicity, even though audiograms were performed every 2 weeks.* Thirteen of the latter patients received the drug for over 6 months and 4 of them received it for 12 or more months. Pyrazinamide has proved to be the most toxic drug and the only one to which fatalities are attributable. Although it might be supposed that fatal hepatotoxicity might also have been the result of homologous serum infection following blood transfusions, it is noteworthy that there were no fatalities in the group of patients who received other drugs. One patient who died of hepatotoxicity had pre-existing Laennec's cirrhosis.

TABLE IV. INCIDENCE OF SEVERE TOXICITY*

	AMI	CYC	KAN	OXY	PRO	PZA	VIO
Patients treated	10	86	35	5	35	114	87
Toxic reactions	1	9	2	0	1	13	11

**Legend:* AMI—amithiozone; CYC—cycloserine; KAN—kanamycin; OXY—oxytetracycline; PRO—Promizole; PZA—pyrazinamide; VIO—viomycin.

TABLE V. SEVERE TOXIC MANIFESTATIONS

DRUG	NUMBER	MANIFESTATION
Amithiozone	1	Elevated Bromsulphalein
Cycloserine	3	Unconsciousness
	2	Dizziness
	2	Psychosis
	1	Convulsion
	1	Leukopenia
Kanamycin	2	Hearing loss (audiometry)
Promizole	1	Hemolytic anemia
Pyrazinamide	10	Elevated Bromsulphalein
	2	Fatal hepatotoxicity
	1	Fever
Viomycin	7	Rash, dizziness, nausea
	2	Elevated blood urea nitrogen
	1	Hematuria
	1	Hearing loss (audiometry)

Emergence of Bacterial Resistance.—Table VI summarizes data regarding the emergence of resistant organisms to cycloserine, kanamycin, and viomycin. The numerals in the table represent the number of patients whose organisms were tested in vitro for evidence of sensitivity to the drug listed on the left. The numbers in parentheses represent those found to be resistant. The drugs listed in the heading of the table are those which were administered in combination with the drugs listed in the left column. It would appear that viomycin did not prevent the emergence of strains resistant to cycloserine. Apparently,

*Since this paper was written one patient developed tinnitus and hearing loss after having received kanamycin, 0.5 Gm. daily, for 9 months.

TABLE VI. EMERGENCE OF RESISTANT

DRUG	DURATION OF											
	1-4						5-8					
	COMBINED WITH						COMBINED WITH					
	ALONE	CYC	PRO	PZA	VIO	OTHER	ALONE	CYC	PRO	PZA	VIO	OTHER
Cycloserine	3 (1)		3 (0)	2 (0)	6 (1)	5 (0)	3 (1)				6 (2)	
Kanamycin	1 (1)	1 (0)	2 (0)				2 (1)	1 (1)	2 (0)	1 (1)		
Viomycin	2 (1)	12 (1)		10 (0)			1 (1)	10 (2)		12 (1)		

Note: See text.
*Legend: CYC—cycloserine, PRO—Promizole, PZA—pyrazinamide, VIO—viomycin.

cycloserine and pyrazinamide did not prevent the emergence of organisms resistant to kanamycin or viomycin. However, these results should be interpreted with the knowledge that organisms resistant to viomycin by standards accepted for this study were obtained from 14 per cent of 80 patients who had never received the drug. Similarily, organisms resistant to cycloserine were obtained from 5 per cent of 41 patients who had not been previously treated with that drug. Tests of susceptibility to kanamycin are considered more reliable since none of 20 previously untreated patients yielded resistant organisms. This does not include patients infected with atypical acid-fast bacilli.

It is notable that viomycin or cycloserine can be administered for prolonged periods without the appearance of strains resistant to 25 mcg. per milliliter. This may possibly be the result of some of the patients' failure to achieve high enough tissue drug levels to eliminate selectively organisms which will not grow in vitro in concentrations of 25 mcg. per milliliter. Blood levels of cycloserine in a few selected patients of this series ranged usually between 15 and 20 mcg. per milliliter. Storey[18] reported an average peak level of 17 mcg. per milliliter 4 hours after the morning dose.

Since few patients receiving SM, PAS, or INH in combination with "secondary" drugs remained infectious for more than a short time, it has not been possible to accumulate much information on the emergence of organisms resistant to the first three drugs. It is significant, however, that 2 patients receiving SM and Promizole yielded organisms resistant to 10 mcg. per milliliter of SM within 2 months of the start of therapy.

Although most of the patients in this series harbored organisms resistant to streptomycin, none was found to have kanamycin-resistant organisms prior to therapy with the latter drug except 2 infected with atypical acid-fast bacilli. These 2 patients had organisms resistant to kanamycin; and one had organisms resistant also to viomycin. Three patients receiving kanamycin developed organisms resistant to both kanamycin and viomycin. Two patients receiving viomycin developed organisms resistant to viomycin but not to kanamycin. These findings are somewhat at variance with those of Steenken and associates.[19]

Surgical Considerations.—Since space infections, whether intrapulmonary, intrapleural, or subscapular are not preventable or curable by "secondary" drugs alone, it is of the utmost importance to obliterate such spaces surgically as soon as possible after the inception of drug therapy. Prolonged open drainage has proved ineffective. For this reason, following modified Schede thoracoplasty

VARIANTS OF TUBERCLE BACILLI*

THERAPY (MONTHS)												
	9-12 COMBINED WITH						12 COMBINED WITH					
	ALONE	CYC	PRO	PZA	VIO	OTHER	ALONE	CYC	PRO	PZA	VIO	OTHER
	3 (0)	2 (2)		1 (0)	5 (3)		3 (1)				3 (2)	1 (0)
	4 (3)			7 (2)		2 (0)	1 (0)	4 (2)		1 (0)		

and removal of infected plombs, the wound is closed tightly and suction drainage by catheter is maintained for approximately 7 days. Thereafter a pressure dressing is maintained until all dead space has been permanently obliterated. These precautions have yielded gratifying results.

Of the 15 patients who are still infectious following pulmonary resection, 7 have pleural empyema, which is both preventable and curable by adequate thoracoplasty. A thoracoplasty leaving a small intrapleural space is almost as ineffective as none at all. The need for adequate space-filling thoracoplasty following resection is indicated by the fact that 40 were performed following 134 resections upon infectious patients.

In this series, 51 bilateral procedures were performed for bilateral cavitary disease. Because of limited cardiopulmonary reserve it was frequently necessary to remove cavitary disease by local wedge excision, leaving considerable amounts of solid disease. Dissection was often difficult. Avoidance of major hemorrhage is believed attributable to the use of techniques previously published.[20] At times so much disease was present that roentgenograms (including tomograms and bronchograms) could not be relied upon to identify all of the cavities. Accordingly, it later became a practice to incise the lung in situ over suspected cavities. This technique if carefully performed is quite safe and if no cavity is located the lung can be sutured easily.

Copious bronchial secretions and bronchoscopic evidence of inflammation have rarely proved troublesome. Secretions have been easily controlled by endotracheal aspiration. Tracheotomy was occasionally necessary. Mechanically assisted ventilation was employed following two operations.

DISCUSSION

The drug regimens employed in this series have proved of the utmost value in the prevention of tuberculous complications following surgery. Their value is indeed even more significant when one considers that they make possible curative surgery in a group of patients who are otherwise incurable. The limits of contemporary pulmonary surgery are now determined almost completely by the patients' cardiopulmonary reserve, complicating disease, and ability to cooperate.

The rather high incidence of toxicity of some of the drugs requires assiduous vigilance. Those which appear most dangerous are amithiozone and pyrazinamide; and for this reason they should probably be used only

for short-term therapy. The toxic and therapeutic dosages of viomycin and cycloserine appear to be very similar. Suggestions have been made to increase the dosage of cycloserine employing other agents to combat toxicity.[21] Another possibility would be to employ 3 drugs. Kanamycin has not proved to be very toxic in the dosage of 0.5 Gm. a day. It is effective in vitro in concentrations as low as 1.25 meg. per milliliter, well below the peak serum levels in patients receiving 0.5 Gm. parenterally.[22] Although Promizole is well tolerated, it is of doubtful value. Our laboratory has shown that inhibition of growth of tubercle bacilli in vitro requires concentrations of Promizole 10 to 40 times as great as are commonly found in the serum of patients receiving 6 grams of the drug a day.

SUMMARY

One hundred and ninety patients were treated with various drug regimens including amithiozone, cycloserine, kanamycin, oxytetracycline, Promizole, pyrazinamide, and viomycin. Nonsurgical treatment yielded poor results. Pulmonary resection early in the course of drug therapy yielded the best results. One hundred and sixty-seven pulmonary resections were performed upon 147 patients with a postoperative tuberculous complication rate of 12.6 per cent and a patient mortality rate of 7.4 per cent. One hundred and thirty-four pulmonary resections were performed upon infectious patients with a postoperative complication rate of 15.7 per cent. Promizole appears to be ineffective; kanamycin appears most promising. Patients should be carefully observed because of drug toxicity. Certain important technical aspects of surgery are discussed.

REFERENCES

1. Matthews, J. H.: Pyrazinamide-INH in the Treatment of Pulmonary Tuberculosis, Trans. Eighteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army and Navy, 1959, p. 106.
2. Storey, P. B.: Cycloserine-Isoniazid Compared With Isoniazid-PAS in the Treatment of Cavitary Pulmonary Tuberculosis, Trans. Eighteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army and Navy, 1959, p. 113.
3. McLean, R. L., and Benson, W. P.: Viomycin and Pyrazinamide in Far Advanced, Drug Resistant Pulmonary Tuberculosis, Trans. Fifteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army and Navy, 1956, p. 122.
4. Moyer, R. E., and Schwartz, W. S.: Pyrazinamide and Cycloserine in the Treatment of Pulmonary Tuberculosis, Trans. Sixteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army and Navy, 1957, p. 59.
5. Moyer, R. E., and Schwartz, W. S.: Cycloserine and Viomycin in the Treatment of Pulmonary Tuberculosis, Trans. Seventeenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army and Navy, 1958, p. 35.
6. Committee of Chemotherapy for Tuberculosis: Clinical Studies of Kanamycin Treatment of Pulmonary Tuberculosis, Ann. New York Acad. Sc. **76**: 166, 1958.
7. Simpson, D. G., Nash, E. S., Riley, E. A., Jones, J. M., and McClement, J. H.: Kanamycin in the Treatment of Pulmonary Tuberculosis, Trans. Eighteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army and Navy, 1959, p. 335.
8. Feldman, W. H., Hinshaw, H. C., and Pfuetze, K. H.: Present Status of Chemotherapy in Tuberculosis, Ann. Int. Med. **22**: 696, 1945.
9. Lincoln, E. M., Stone, S., and Hoffman, O. R.: The Treatment of Miliary Tuberculosis With Promizole, Bull. Johns Hopkins Hosp. **82**: 56, 1948.

10. Hinshaw, H. C., and McDermott, W.: Thiosemicarbazone Therapy of Tuberculosis in Humans, Am. Rev. Tuberc. **61**: 145, 1950.
11. Miller, F. L., Sands, J. H., Gregory, L. J., Hightower, J. A., Weiser, O. L., and Tempel, C. W.: Daily Oxytetracycline (Terramycin) and Intermittent Streptomycin in the Treatment of Pulmonary Tuberculosis, Am. Rev. Tuberc. **69**: 65, 1954.
12. Pecora, D. V., and Yegian, D.: The Significance of Bacterial Resistance to Drugs in Pulmonary Resections for Tuberculosis, Am. Rev. Tuberc. **75**: 781, 1957.
13. Pecora, D. V.: Pyrazinamide and Viomycin in the Surgical Treatment of Pulmonary Tuberculosis, Am. Rev. Tuberc. **77**: 83, 1958.
14. Webb, W. R.: Pulmonary Resection for Drug-Resistant Cavitary Tuberculosis Utilizing Ancillary Drugs, Am. Rev. Tuberc. **79**: 780, 1959.
15. Yeager, R. L., Munroe, W. G. C., and Dessau, F. I.: Pyrazinamide (Aldinamide) Experience in the Treatment of Pulmonary Tuberculosis, Am. Rev. Tuberc. **65**: 523, 1952.
16. Monaldi, V.: Tentativi di asperazione endocavitaria nelle caverne tubercolari del polmone, Lotta contro la tuberc. **9**: 910, 1938.
17. Grow, J. B.: Chronic Pleural Empyema, Dis. Chest **12**: 26, 1946.
18. Storey, P. B.: Discussion, Trans. Seventeenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army and Navy, 1958, p. 40.
19. Steenken, W., Jr., Montalbine, V., and Thurston, J. R.: The Antituberculous Activity of Kanamycin in Vitro and in the Experimental Animal (Guinea Pig), Am. Rev. Tuberc. **79**: 66, 1959.
20. Pecora, D. V.: Vascular Accidents During Pulmonary Resection: Prevention and Care, Surgery **38**: 1134, 1955.
21. Pyle, M. M., Pfuetze, K. H., Barclay, W. R., and Kasik, J. E.: Cycloserine in High Dosage in "Salvage Cases" of pulmonary Tuberculosis With Control of Toxicity by Concomitant Medication: Efficacy as Medical and pre-Surgical Treatment, Trans. Eighteenth Conference on the Chemotherapy of Tuberculosis, Veterans Administration, Army and Navy, 1959, p. 128.
22. Wright, K. W., Renzetti, A. D., Jr., Lunn, J., and Bunn, P.: Observations on the Administration of Kanamycin to Patients With Tuberculosis, Am. Rev. Tuberc. **79**: 72, 1959.

CHEMICAL AND SURGICAL REMOVAL OF EPICARDIUM AND VISCERAL PLEURA

Frances E. Knock, Ph.D., M.D., and Edward J. Beattie, Jr., M.D., Chicago, Ill.

MANY TISSUES have been used as sources of extracardiac blood supply to ischemic myocardium in the surgical treatment of coronary artery insufficiency. Whatever the tissue used, the smooth epicardium prevents firm adhesion of such tissue to underlying myocardium.

When lung and abraded pericardium were used as sources of extracardiac blood, no change was noted by us in the results following use of either irritants, such as talc and asbestos, or growth-promoting substances, such as chick embryo extract, pituitary growth hormone, mineral corticoids, or thyroxin-like compounds. Poor adhesions resulted also when the growth-promoting substances were applied to Ivalon sponge and the sponge sutured between smooth epicardium and either lung or abraded pericardium.

Omentum can be used as a source of new blood vessels to the heart.[1-4] When omentum is sutured to the heart without removal of epicardium, simple digital pressure allows easy stripping of omentum from the heart even if heart and omentum have been in contact for months. However, if epicardium is first removed before omentum is sutured to the denuded myocardium, the omentum will tear before it can be stripped off the heart. The results are the same whether or not irritants such as talc and asbestos are used between omentum and heart.

Surgical removal of epicardium is relatively simple for the left ventricle but difficult for the right ventricle. As a result, chemical methods for removal of epicardium became of interest. Many aliphatic and aromatic compounds have been tested in our laboratories for chemical removal of epicardium.[2] Of these, the most useful has been sodium salicylate in various hypertonic solutions. Five per cent sodium salicylate in 25 per cent glucose was used first to loosen epicardium chemically in preparation for surgical removal.

RESULTS

To demonstrate the depth of tissue removed by the combined chemical and surgical procedure, the heart was covered with gauze sponges which had been soaked in the solution kept at 37° C. Surgical removal of epicardium

From the Department of Surgery, Presbyterian-St. Luke's Hospital, 1753 W. Congress Parkway, Chicago, and the University of Illinois College of Medicine, Chicago, Ill.

This work was supported by research grants from the Department of Surgery, Presbyterian-St. Luke's Hospital, and the U. S. Public Health Service.

Received for publication Jan. 25, 1960.

Fig. 1.

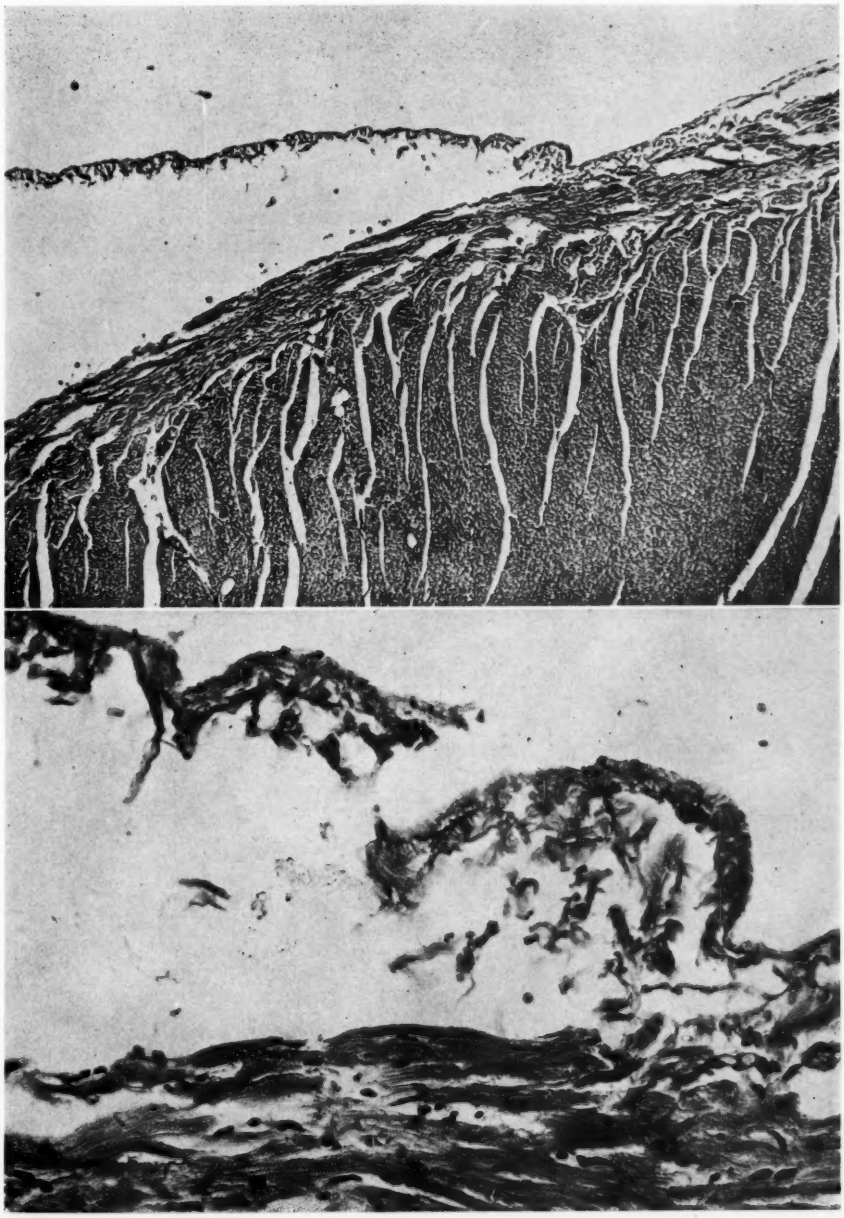


Fig. 2.

Fig. 1.—Epicardium lifted off the myocardium surgically after treatment with 5 per cent sodium salicylate in 25 per cent glucose.

Fig. 2.—Junction of leading edge of epicardium with the myocardium.

Fig. 3.

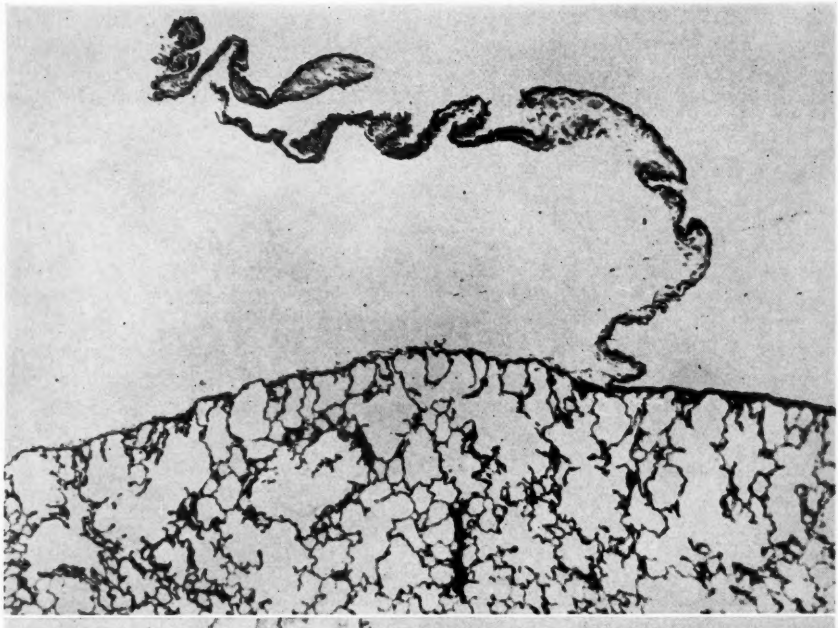


Fig. 4.

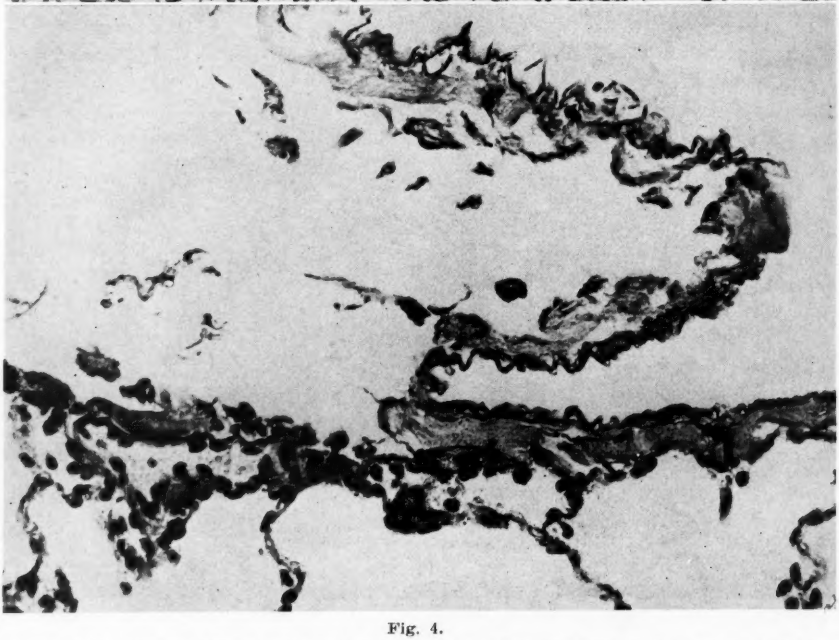


Fig. 3.—Visceral pleura lifted off lung surgically after treatment with 5 per cent sodium salicylate in 25 per cent glucose.

Fig. 4.—Junction of leading edge of visceral pleura with lung.

was begun 3 to 5 minutes after application of the solution to the heart. Histologic sections were then taken at the junction of denuded myocardium with the flap of epicardium which had been lifted off the myocardium.

In Figs. 1 and 2 are shown microscopic sections of the leading edge of removed epicardium. All sections show remarkably little damage to underlying myocardium.

Most patients with coronary artery disease who require surgery will have been digitalized completely at the time of surgery. Intravenous infusions of glucose in digitalized patients may precipitate runs of ectopic ventricular beats, presumably due to reduction in serum potassium.[5] As a result, hypertonic glucose solutions should be applied to the hearts of such patients with caution.

Sodium salicylate solutions can be used alone for loosening of epicardium but appear to act slightly more rapidly and effectively in combination with other hypertonic solutions. When compared with glucose, other compounds at osmotically equivalent concentration, such as fructose, galactose, and urea, act essentially as does the glucose and will probably be more useful for application to diseased hearts.

The same solutions, which loosen epicardium and facilitate its surgical removal, act similarly on visceral pleura. In Figs. 3 and 4 are shown microscopic sections of the leading edge of visceral pleura being lifted off the underlying lung.

Surgical removal of visceral pleura is considerably more difficult and time consuming than removal of epicardium and requires longer contact of the lung with sodium salicylate solutions (5 to 10 minutes). Again, the sections show a remarkable lack of damage to underlying alveoli.

CONCLUSIONS

Attempted revascularization of the heart by bringing to it a new source of blood supply may or may not have value. Experimental studies in our laboratory appear to indicate benefit.[2-4]

The epicardium must be removed if suitable adhesions are to form. Surgical removal of the epicardium, especially from the right ventricle, is difficult and may be hazardous. Chemical loosening of the epicardium facilitates its removal. The use of sodium salicylate has proved successful and safe in the experimental animal.

The possibility that chemical loosening of dense scarring may make possible otherwise hopeless decortication of the lung and heart is being investigated.

REFERENCES

1. O'Shaughnessy, L.: Surgical Treatment of Cardiac Ischaemia, Lancet **1**: 185-194, 1937.
2. Knock, F. E.: Cardioomentopexy and Implantation of Multiple Omental Loops for Revascularization of the Heart, Surg. Forum **9**: 230-232, 1958.
3. Knock, F. E.: Comparison of Radical Cardioomentopexy With the Beck I and Vineberg Sponge Operations for Revascularization of the Heart, Surg. Forum **10**: 626-629, 1959.
4. Knock, F. E., and Beattie, E. J.: Myocardial Revascularization—A Comparative Study, Proc. Inst. Med. Chicago (In press).
5. Priebe, F. H.: Ventricular Arrhythmias Due to Glucose, J. Indiana M. A. **52**: 205-206, 1959.

THE EFFECTS OF LARGE DOSES OF NORETHANDROLONE ON NITROGEN BALANCE IN PATIENTS UNDERGOING PULMONARY RESECTION FOR TUBERCULOSIS

John Hines Kennedy, M.D., and Harold G. Peters, M.D.,*
San Diego, Calif.

IN A PREVIOUS communication,[1] the authors have reported the failure of currently accepted doses of the synthetic steroid norethandrolone (17α-ethyl-17-hydroxynorandrostenone) to bring about a return to positive nitrogen balance in patients who underwent pulmonary resection for tuberculosis. This is a report of the use of large doses of norethandrolone, 100 mg. per day, in 5 clinically well-nourished patients who underwent pulmonary resection for tuberculosis.

MATERIALS AND METHOD

Nine clinically well-nourished patients without complicating medical disorders, other than pulmonary tuberculosis, who were scheduled to undergo elective pulmonary resection were selected for study and placed at random into two groups. After a preoperative control balance period of 3 days, the 5 patients in the study group received norethandrolone (Nilevar), 100 mg. by intramuscular injection daily, through the twelfth postoperative day. The patients in the control group received a placebo. The total period of observation was 15 days. Patients with all degrees of severity of pulmonary tuberculosis, who had achieved sputum conversion on antitubercuous chemotherapy preoperatively, were included in the study.

All patients were given a 2,500 calorie diet high in protein, and analysis of the uneaten food for total nitrogen was used to arrive at an accurate estimate of total nitrogen intake. An estimate of nitrogen balance was calculated by comparing the total nitrogen excretion in pooled homogenized 3-day collections of pleural fluid, urine, and feces, as compared with the total nitrogen intake in pooled homogenized 3-day duplicate diet specimens. Collections were made in tared containers and preserved in the frozen state until analysis.

Aliquots of pooled 3-day intake and output specimens to which had been added an antifoam preparation were analyzed for total nitrogen intake by

Received for publication Jan. 29, 1960.
*At present, Senior Registrar in Thoracic Surgery, Frenchay Hospital, Bristol, England.

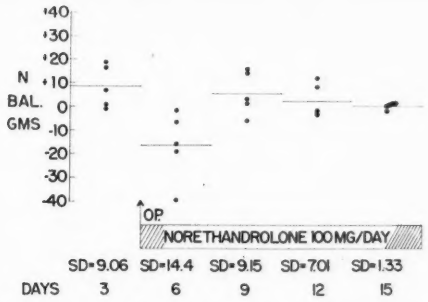


Fig. 1.—Nitrogen balance in 5 patients undergoing surgery for pulmonary tuberculosis who received norethandrolone. Mean nitrogen balance is indicated by the horizontal black lines.

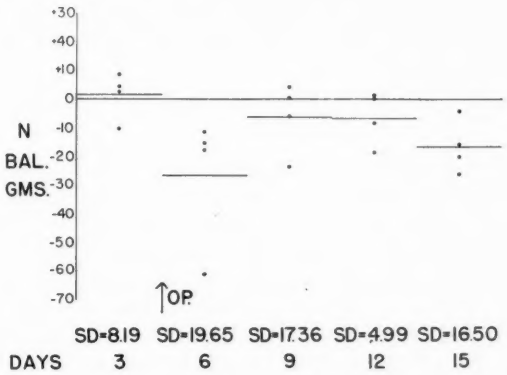


Fig. 2.—Nitrogen balance in 4 patients undergoing surgery for pulmonary tuberculosis (controls). Mean nitrogen balance is indicated by the horizontal black lines.

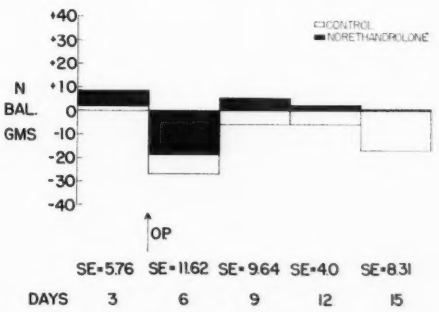


Fig. 3.—A comparison of the mean nitrogen balance between the control and experimental groups. The standard error of the difference between two means (S. E. D.) is recorded.

digestion and nesslerization, and nitrogen analyses were carried out by comparison with the standard nitrogen solution using a Beckman spectrophotometer, Model B.

Four of the 9 patients were in negative nitrogen balance in the preoperative period before the study was initiated. The nitrogen balances of the 5 patients who received norethandrolone are recorded in Fig. 1. It will be noted that the mean nitrogen balance showed an anticipated fall following surgical trauma,[2, 3, 4] but that there was a prompt return to positive nitrogen balance between the sixth and ninth day of study. A calculation of the standard deviation from these mean values is recorded. In Fig. 2 the nitrogen balances of the 4 patients who received a placebo are recorded. These control patients again showed an abrupt negative nitrogen balance in response to surgery but remained in negative nitrogen balance and had not returned to the positive state by the conclusion of the study. Fig. 3 shows a graphic comparison of the mean nitrogen balances for the control group and the group which had received norethandrolone. A calculation of the standard error of the difference between two means suggests that this is a statistically significant difference in the last two balance periods.

DISCUSSION

Allowing for the small size of this sample, patients undergoing pulmonary resection for tuberculosis showed a marked anabolic response to norethandrolone in doses of 100 mg. daily for 12 days postoperatively. An application of the statistical method suggests that this is a significant difference as compared to control patients who received a placebo. No current explanation is available to date for the relatively refractory catabolic state of tuberculous patients. It has been surmised that patients subjected to the chronic stress situation of pulmonary tuberculosis to which is added the insult of surgery require a proportionately larger amount of an anabolic agent to effect positive nitrogen balance. The urinary 17-hydroxycorticosteroid excretion in these patients is being studied at present.

SUMMARY

This is a report of the use of large doses of norethandrolone, 100 mg. per day, in 5 clinically well-nourished patients who underwent pulmonary resection for tuberculosis. Patients were placed in control and experimental groups and, after a control preoperative balance period, were given 100 mg. of norethandrolone daily by injection for 12 days following surgery. Four control patients received a placebo. Four of 5 patients in the experimental group were in positive nitrogen balance at the conclusion of the study. The 4 patients who served as controls remained in negative nitrogen balance and did not return to their preoperative level of nitrogen balance at the end of the experimental period. An application of the principle of the standard error of the difference between two means suggests that this is a statistically significant difference, allowing for the small size of the sample.

The authors wish to acknowledge the cooperation of Dennis Fox, Ph.D., Professor of Marine Biological Chemistry at Scripps Oceanographic Institute of the University of California at La Jolla, and the technical assistance of Michael Pilson, B.S., M.S., who carried out the nitrogen analyses.

The norethandrolone used in this study was supplied by G. D. Searle and Co., Chicago, Ill.

REFERENCES

1. Kennedy, J. H., Peters, H. G., and Serif, G. S.: Observations on The Effect of Norethandrolone in Favoring Anabolism in Patients Undergoing Pulmonary Resection for Tuberculosis, S. Forum **9**: 364-367, 1959.
2. Moore, F. D., and Ball, M. R.: Metabolic Response to Surgery, Springfield, Ill., 1952, Charles C Thomas, publisher.
3. Abbott, W. E., Libby, S., Harvey, K., Benson, J. W., and Rayburn, C. J.: The Effect of Depotestosterone Derivatives on Nitrogen Balance and Body Weight in Postoperative Patients, Proc. Surg. Forum, Am. Coll. Surgeons, Philadelphia, 1956, W. B. Saunders Company.
4. Glider, H., Free, E. A., Weeks, D. L., and Beal, J. M.: The Effects of Hormones on the Surgical Patients, Proc. Surg. Forum, Am. Coll. Surgeons, Philadelphia, 1956, W. B. Saunders Company.

SOME EXPERIMENTAL OBSERVATIONS ON THE SUPERIOR VENA CAVA–PULMONARY ARTERY ANASTOMOSIS

*Xavier Palacios-Macedo, M.D.,*Juan J. Pérez-Alvarez, M.D.,* Julio Ortiz-Márquez, M.D.,** and Julio Hernández-Peniche, M.D.,****
México City, México

SEVERAL surgical groups in different countries have reported both experimental and clinical work on superior vena cava–pulmonary artery anastomosis for the treatment of certain cyanotic congenital malformations of the heart.[1-4]

The operation consists of an end-to-end anastomosis of the distal ends of the superior vena cava and the right pulmonary artery, thus bypassing the right side of the heart and increasing the flow of venous blood directly to the lung.

Since the data contained in some of the available literature seemed to us contradictory or incomplete, and since we considered the procedure based on sound theoretical principles, the present study was undertaken to determine the modifications caused by the operation on different parameters regarding which we were still in doubt.

MATERIAL AND METHOD

Twelve mongrel dogs were used. Before performing the anastomosis, control tests were made on 10 dogs to study the changes produced by the occlusion of the right pulmonary artery, and especially those produced by the occlusion of the superior vena cava.

Technique.—Under intravenous sodium Kemithal anesthesia, an endotracheal tube was inserted and connected to an oxygen-delivering mechanical respirator. The anesthesia was continued with supplementary doses of intravenous Kemithal on 9 dogs, and on the other 2 animals ether-oxygen was utilized. Cannulation of the external jugular vein and of the femoral vein was carried out with catheters introduced into the superior and the inferior venae cavae, respectively, and connected to water manometers. The femoral artery was cannulated, and the catheter connected to the electromanometer. The animal was attached to the electrocardiograph and the electroencephalograph. Through the

From the Hospital de La Raza (Instituto Mexicano del Seguro Social), México City, México.
Received for publication Jan. 12, 1960.
*Department of Cardiovascular Surgery, Hospital de La Raza.
**Department of Cardiology, Hospital de La Raza.
***Department of Neurology, Hospital de La Raza.

right fourth intercostal space, a posterolateral thoracotomy was performed, the azygos vein dissected free and ligated, the superior vena cava freed down to its junction with the right auricle, and the right pulmonary artery dissected all the way out to the bifurcation of the main pulmonary artery, where it was transected between two atraumatic clamps and its proximal end was ligated. The superior vena cava was then also transected between clamps, and its auricular orifice sutured. The distal ends of these two vessels were then united with a continuous running stitch of 5-0 arterial silk, and the occluding clamps were released.

The technique of anastomosis just described was used on 8 animals. On another 2, the only variant was that the azygos vein was not ligated until after the anastomosis had been completed and the occluding clamps were released. On 1 animal, an end-to-end anastomosis was made, between the proximal end of the azygos vein and the distal end of the right pulmonary artery, as advocated by Glenn.[5] Finally, on 1 dog, an end-to-side anastomosis was made between the distal end of the pulmonary artery and the side of the superior vena cava, with occlusion of the latter below the anastomosis after this was completed.

RESULTS

1. *Arterial Pressure.*—In 9 cases, the occlusion of the superior vena cava produced immediate but slight reduction of the arterial pressure which remained stable after this, and throughout the entire period of occlusion. The re-opening of the superior vena cava in these cases was followed by an immediate return of the arterial pressure to approximately the values observed prior to the occlusion. We shall refer hereinafter to these cases as those in which there was a "slight reduction of the arterial pressure." In 3 cases, the slight reduction observed immediately after the occlusion of the superior vena cava was followed by a progressive and important further reduction of the arterial pressure, until it reached a mean of 30 mm. Hg within an average time of 20 minutes. We shall refer to these cases as those in which there was a "severe reduction of the arterial pressure." In this group of animals, the arterial pressure returned to normal levels as the superior vena cava was released, but again it reached very low figures after re-occluding this vessel. However, it was possible to keep it stable, and around normal values, by means of intravenous administration of norepinephrine, without having to unclamp the superior vena cava.

2. *Superior Vena Cava Pressure.*—The pressure of the superior vena cava increased rapidly after the occlusion of the vessel, and it reached its maximum within an average time of 2 minutes. The maximal range was from 38 to 85 cm. H_2O. In the animals in which a "slight reduction of the arterial pressure" was observed, the venous pressure remained stable around the figures reached immediately after the occlusion. On the contrary, in the animals in which a "severe reduction of the arterial pressure" was present, the venous pressure curve had the following pattern: after reaching a maximum, soon after the occlusion of the vena cava, there was a progressive reduction of the venous

pressure that was proportional to the reduction of the arterial pressure. The unclamping of the vena cava, or the administration of norepinephrine—besides producing a re-establishment of a normal arterial pressure—made the venous pressure return to the high levels reached immediately after the occlusion of the vena cava. Once the anastomosis was completed and the clamp removed from the vena cava, the venous pressure in this vessel dropped, although in none of the animals did it return to normal, the range being from 18 to 23 cm. H_2O. These facts are illustrated in Fig. 1.

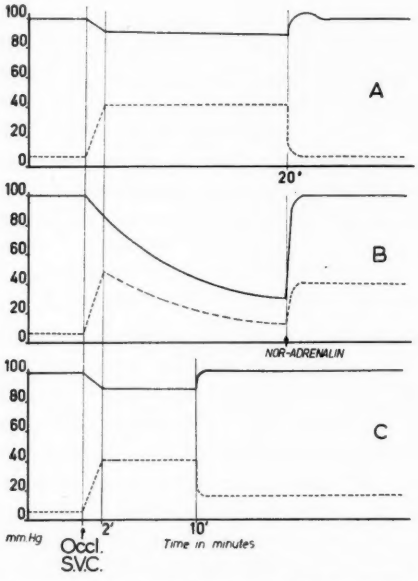


Fig. 1.—Schematic representation of the changes in the mean arterial and venous pressures in millimeters of mercury. *A*, Before, during, and after a 20-minute occlusion of the superior vena cava in a case of slight reduction of the blood pressure. *B*, Before and during a 20-minute occlusion of the superior vena cava in a case of severe reduction of the blood pressure and after administration of noradrenalin. *C*, Before, during, and after the performance of a superior vena cava–pulmonary artery anastomosis with slight reduction of the arterial pressure.

3. *Inferior Vena Cava Pressure.*—A slight reduction of the pressure in the inferior vena cava was observed during the period of occlusion in all of the cases. The original pressure averaged 9 cm. H_2O, and it lowered to an average of 6 cm. H_2O.

4. *Electroencephalogram Utilizing Four Cephalic Electrodes With Eight Leads.*—In the group of 9 animals that had a "slight reduction of the arterial pressure," the EEG remained normal or only showed unimportant modifications despite very high venous pressures (in one case up to 85 cm. H_2O). On the contrary, in the group of 3 animals that had a "severe reduction of the arterial pressure," the EEG showed important changes, consisting of slowing and voltage reduction of the tracing at the beginning, followed by complete flattening of the same, with bursts of periodic activity. When the arterial pressure reached normal limits, either as a result of unclamping the superior vena cava or the

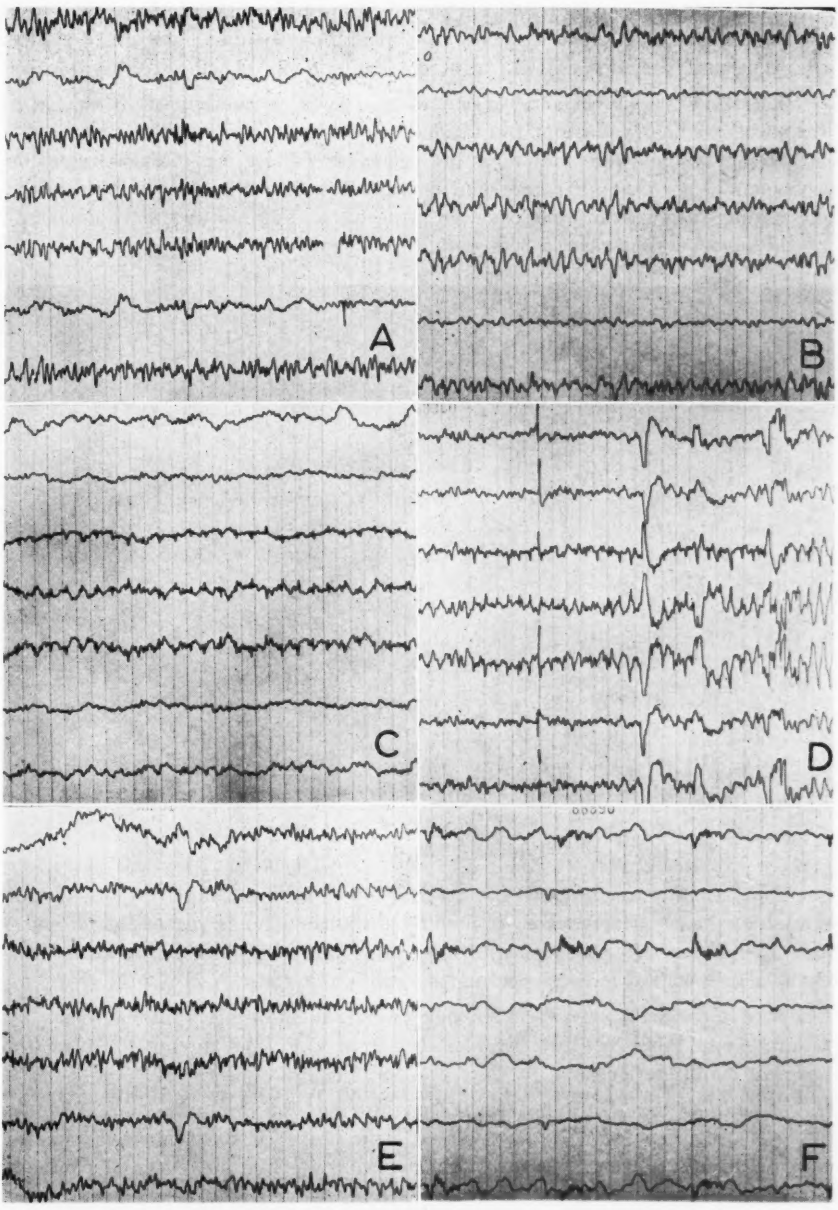


Fig. 2.—Electroencephalograms. *A*, Control tracing during anesthesia with sodium Kemithal. *B*, Tracing unchanged. Arterial pressure, 140/90 mm. Hg; venous pressure 59 cm. H_2O. *C*, Flattening of the tracing. A case in which the arterial pressure dropped to 55/30 mm. Hg; venous pressure 50 cm. H_2O. *D*, Recovery 15 seconds after raise of arterial pressure to 80/55 mm. Hg; venous pressure, 55 cm. H_2O. *E*, Tracing showing no alterations in a case of venous pressure of 85 cm. H_2O and arterial pressure of 140/90 mm. Hg. *F*, Complete flattening of the tracing with bursts of periodic activity in a case of sustained arterial hypotension.

action of vasopressors, the records returned to normal within a period of 1 to 2 minutes (Fig. 2). It is worth mentioning that these 3 animals were in a rather precarious nutritional condition, although without any other apparent disease.

5. *Oximetry.*—Oxygen saturation of the blood in the superior vena cava was measured before, during, and after the occlusion of this vessel. The following average values were found: before occlusion, 63 per cent; 5 minutes after occlusion, 36 per cent; 15 minutes after occlusion, 35 per cent; 5 minutes after unclamping the superior vena cava, 68 per cent; and 15 minutes after unclamping the superior vena cava, 64 per cent.

Fig. 3. Fig. 4. Fig. 5.

Figs. 3, 4, and 5.—See text.

The oximetry readings in the arterial blood, taking samples before the occlusion of the superior vena cava, 5 and 15 minutes after it was occluded, and 5 and 15 minutes after occlusion of the right pulmonary artery, remained unchanged and stable above 95 per cent.

6. *Electrocardiogram.*—No changes worth mentioning, that could be attributable to the procedure, were observed at any time during or after the surgical manipulations.

7. *Angiograms.*—Angiograms taken during the occlusion of both the superior vena cava and the azygos vein show filling of the vena cava and the internal mammary and vertebral veins with dye (Fig. 3). The films taken during the occlusion of the vena cava alone, leaving the azygos vein unoccluded, show filling of the azygos vein system especially, and a small amount of dye going into the vertebral veins (Fig. 4). The angiograms taken several days after the anastomosis had been performed show filling of the pulmonary vessels with dye, and also some filling of the vertebral veins (Fig. 5).

8. *Pressure Tracings.*—Pressure tracings obtained postoperatively from the right and left pulmonary arteries are illustrated in Fig. 6. There is a slight reduction of the mean right pulmonary artery pressure, with loss of its characteristic pattern, that is, without systolic and diastolic oscillations.

DISCUSSION

In normal conditions, the blood collected in the venae cavae requires the propulsion of the right ventricle in order to reach the pulmonary capillaries. The right ventricle provides the force to propel the blood from the vessel in which the pressure is around 3 mm. Hg, to another in which the mean pressure is around 18 mm. Hg.

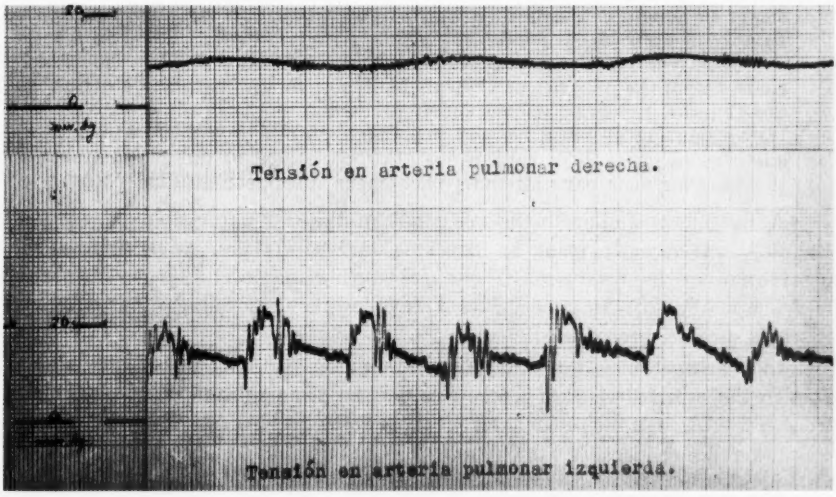


Fig. 6.—Pressure curves taken 15 days postoperatively from the right pulmonary artery (*upper tracing*) and the left pulmonary artery (*lower tracing*). See text.

When the pulmonary artery is disconnected from the source of energy that maintains that pressure, a much lower one is sufficient to make the blood progress into the pulmonary circulation, since normally the pressure in the left auricle is only about 5 mm. Hg. The average pressure in the superior vena cava, observed in our animals after the operation was performed, was 19 cm. H_2O, or 14 mm. Hg.

Our findings are in accordance with those of Robicsek[1, 2] and Bakulev[3] and their associates in this respect, as well as with regard to the maintenance of the permeability of the anastomosis. There are, however, several points in which our experience differs from that of the Russian author. We are aware of the fact that Bakulev's report deals with cyanotic patients who already have a deficient arterial oxygen saturation due to venous-arterial shunts. This fact may perhaps explain some of the differences with our experimental results, but others require an explanation different from the one proposed by this investigator.

Bakulev[3] reports:

> Observation of patients during operation reveals marked hemodynamic changes, especially after the clamping of the superior vena cava. Arterial blood pressure in all these patients drops somewhat while the superior vena cava and the pulmonary artery are being dissected out. Clamping of the superior vena cava causes no further drop. But the venous blood pressure, at this moment, shoots up to 500 to 600 mm. H_2O. Oxygen saturation begins to drop during the dissection of the major vessels, which is explained by their temporary occlusion during this stage of the operation. Oximeter readings show a more marked drop when the pulmonary artery is tied and especially when the superior vena cava is clamped. At this moment, the oximeter readings go down from 90 per cent to 30 per cent and even beyond. Once the clamp on the superior vena cava is off and the newly created anastomosis starts to function, the blood oxygen figures begin to rise and return rapidly to their initial level.
>
> Electroencephalographic studies, carried out during these operations, reveal the presence of typical changes. During the placing of the anastomosis, signs of hypoxia and hypercapnia of the brain supervene. Depression of the brain centers progresses. Voltage is decreased and silent zones make their appearance. After removal of the clamp from the superior vena cava all these phenomena disappear gradually.

A statement, similar to the one made in the last paragraph quoted from Bakulev, was recently made by Brechner and co-workers,[6] who reported the observation of important EEG changes during the occlusion—even partial and temporary—of the superior vena cava, while performing different intrathoracic surgical procedures.

In our experience, there was the outstanding fact that although the pressure in the superior vena cava was raised greatly, no substantial EEG changes were observed. On the other hand, in those cases in which the arterial pressure was lowered considerably (the venous pressure remaining higher than normal, although lower than immediately after the occlusion of the superior vena cava), severe EEG changes appeared, and after a few minutes the cerebral activity ceased. Moreover, these phenomena regressed in an identical form after the unclamping of the superior vena cava, or when the arterial pressure was maintained within reasonable limits by means of the administration of vasopressors, despite a persistent high venous pressure (see Fig. 1). To us, the explanation of these facts lies in the severe reduction of the arteriovenous pressure gradient in the brain.

Normally, the cerebral arteriovenous pressure gradient is very large (see Fig. 7). It can be stated that there is a great mechanical facility for the flow of blood through the brain. In addition, the compensatory mechanisms of the brain adapt themselves very readily to changes in the blood flow. The occlusion of the superior vena cava produces a reduction of the pressure in the afferent vessels, and a rise in the pressure in the vessels leaving the brain, thus producing a reduction of the arteriovenous pressure gradient, and a consequent reduction of the velocity of the flow of blood through the brain. This permits an increase in the extraction of oxygen from the blood by this organ, a fact that is manifest by the reduction in the oxygen saturation of the superior vena cava blood from 63 per cent before its occlusion to 35 per cent after 15 minutes

of occlusion, the arterial oxygen saturation remaining normal throughout. It is not until these pressure changes reach a certain point that the circulation in the cerebral vessels stops or becomes so slow that suffering of the brain supervenes.

From the results of our experiments we think that the EEG changes are not a consequence of the elevated venous pressure, as suggested by Bakulev and Brechner, but rather the result of the reduction of the arteriovenous pressure gradient brought about basically by the lowering of the arterial pressure, regardless of the venous pressure values. This seems to us an interesting and important subject for further experimentation.

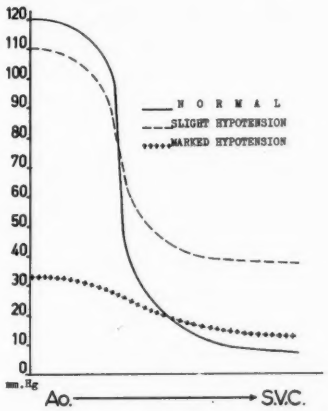


Fig. 7.—Arteriovenous pressure gradient. See text.

During the performance of a superior vena cava–pulmonary artery anastomosis, one must take into account the importance of maintaining a reasonable cerebral arteriovenous pressure gradient in order to avoid damage to the brain. This seems to be the main risk during the performance of this operation. Some of the variants that have been proposed may avoid this. Glenn and co-workers[5] advocated, for instance, the anastomosis of the azygos vein to the pulmonary artery. In the dog in which we performed this variant, as well as in the 1 in which an end-to-side anastomosis between the side of the vena cava and the end of the pulmonary artery was done, the arterial and the venous pressures remained normal throughout the performance of the anastomosis, and only after tying the superior vena cava did the venous pressure rise to 24 cm. H_2O. In the other 2 cases in which the azygos vein was allowed to remain patent until after the completion of the anastomosis, the elevation of the venous pressure and the reduction of the arterial pressure were only slight.

It is our belief that the latter modification of the technique is the one that involves the least technical difficulties, and yet solves the problem adequately. It is possible that, in some human cases, in which the pulmonary artery is hypoplastic and there is a large disproportion between its caliber and that of the superior vena cava, Glenn's technique will be preferable.

In our opinion, if the pressure in the superior vena cava becomes too high after the operation, this may indicate difficulty in the emptying of the superior vena cava into the pulmonary vascular bed. Thrombosis at the site of the anastomosis is then facilitated. On the other hand, the anastomotic collateral veins connecting the superior and the inferior venae cavae systems—shown in the angiograms—will enlarge more readily when subjected to a higher pressure. In these conditions a larger amount of blood will drain into the right auricle as time elapses, and the final result of the operation may be less beneficial than intended, if at all. A situation, similar to the one we just outlined, occurs when the inferior vena cava is ligated in the abdomen as a treatment for intractable congestive heart failure; after a few months, during which the patient may have improved, the development of new collateral vessels, or the enlargement of the previously existing ones, causes the patient to return to his previous condition.

CONCLUSIONS

1. The superior vena cava–right pulmonary artery anastomosis seems to us a physiologic operation that permits an excellent flow of venous blood to the lung, bypassing the right ventricle, and thus reducing the load on this ventricle, when there is an obstacle to its emptying, as happens in the tetralogy of Fallot. Although it is our belief that a complete repair of the malformation, whenever feasible, is the treatment of choice for the tetralogy of Fallot, in those cases in which the dextroposition of the aorta is extreme or the pulmonary artery is hypoplastic, the performance of a superior vena cava–pulmonary artery anastomosis must be considered.

2. We believe this operation is also indicated in the other congenital cardiac malformations (tricuspid atresia, Ebstein's disease, complete transposition of the great vessels) in which the only complete solution would be the total replacement of the heart.

3. The main risk of the operation is, no doubt, the hemodynamic alteration produced on the cerebral circulation during occlusion of the superior vena cava.

4. This alteration seems to be caused by a severe reduction in the cerebral arteriovenous pressure gradient, rather than by the elevation of the pressure in the superior vena cava alone, which was well tolerated by the majority of our dogs.

5. Only the animals in a poor nutritional condition presented "severe reduction of the arterial pressure" which, coincident with an elevated venous pressure, resulted in a reduction of the cerebral arteriovenous pressure gradient in sufficient degree to provoke substantial changes in the EEG.

6. In the normal dog, the occlusion of the superior vena cava produces a considerable reduction in the oxygen saturation of the venous blood tributary of the occluded vessel, but it does not affect the oxygen saturation of the arterial blood, even with the simultaneous occlusion of the right pulmonary artery.

REFERENCES

1. Robicsek, F., Tenesvary, A., and Kadar, R. L.: A New Method for the Treatment of Congenital Heart Disease Associated With Impaired Pulmonary Circulation, Acta med. scandinav. **154**: 151, 1956.
2. Robicsek, F., Magistro, R., Foti, E., Robicsek, L., and Sanger, P.: Vena Cava–Pulmonary Artery Anastomosis for Vascularization of the Lung, J. THORACIC SURG. **35**: 440, 1958.
3. Bakulev, A. N., and Kolesnikov, S. A.: Anastomosis of Superior Vena Cava and Pulmonary Artery in the Surgical Treatment of Certain Congenital Defects of the Heart, J. THORACIC SURG. **37**: 693, 1959.
4. Sanger, P. W., Robicsek, F., and Taylor, F. H.: Vena Cava–Pulmonary Artery Anastomosis. III. Successful Operation in Case of Complete Transposition of Great Vessels With Interatrial Septal Defect and Pulmonary Stenosis, J. THORACIC SURG. **38**: 166, 1959.
5. Glenn, W. W. L., and Patino, J. F.: Circulatory Bypass of the Right Heart. Azygos Vein–Pulmonary Artery Shunt, Yale J. Biol. & Med. **27**: 147, 1954.
6. Brechner, B. L., Kavan, E. M., and Dillon, J. B.: The Electroencephalographic Effect of Compression of the Superior Vena Cava During Thoracotomy, J. THORACIC SURG. **37**: 352, 1959.

HOMOVITAL TRANSPLANTATION OF THE HEART

Richard R. Lower, M.D., Raymond C. Stofer, D.V.M., and*
*Norman E. Shumway, M.D.,** Palo Alto, Calif.*

SUCCESSFUL homologous cardiac transplantation as a practical solution for otherwise irreparable heart disease presents essentially three problems: (1) obtaining and preserving the organ graft in a viable state, (2) a surgical technique for removal and replacement of the heart, and (3) a means of eliminating the homograft rejection phenomenon. The first and third problems must be met presumably at the level of cellular physiology. Preservation of the donor heart implies either maintenance of the normal cellular metabolism in an artificial milieu or complete suspension of metabolism. Current attempts to apply the latter principle are based largely on the use of hypothermia to diminish or abolish cellular requirements. Hypothermia techniques, thus far, have not succeeded in suspending metabolism for prolonged periods without trauma to the organ.

The homograft rejection mechanism can be avoided only when its nature is more clearly defined. Although much information has been acquired concerning the role of desoxyribonucleoproteins, the exact antigenic substance which donor tissue elaborates has not been identified. Further, the precise mechanism by which the host causes death of the homologous cells is not known. One must assume that, as these mechanisms are clarified, an appropriate means will be found of altering either the elaboration of the homologous antigen or the immunologic response of the host without injury to either graft or host.

With regard to the surgical problem, the technique herein described illustrates that it is now feasible to effect a homovital transplantation of the canine heart following removal of the animal's own heart. Early in our experience many unsuccessful attempts were made. A satisfactory procedure evolved which resulted initially in the survival of several animals for 6 to 72 hours and ultimately in the survival of 1 dog for 8 days with complete maintenance of the circulation by the heart graft. This report presents a method which will afford opportunity for further study of the homograft rejection mechanism as it affects transplantation of the entire heart.

From the Department of Surgery, Stanford University School of Medicine, Palo Alto, Calif.
Supported by Research Grants H-3935 and H-4658 of the National Heart Institute.
Received for publication Feb. 9, 1960.
*Research Fellow, National Heart Institute.
**Established Investigator, American Heart Association.

METHOD

The donor animal is anesthetized with 30 mg. per kilogram of intravenous pentobarbital. Ventilation with 100 per cent oxygen is provided by an electronic respirator attached to a cuffed endotracheal tube. Thoracotomy is performed through the left fourth intercostal space. The azygos vein is ligated, and umbilical tapes are passed about the extrapericardial portions of the superior and inferior venae cavae. Heparin, 2 mg. per kilogram, is administered intravenously. Mild hypothermia of the donor animal is produced by the application of ice, and the rectal temperature is permitted to drop approximately to 30° C.

The recipient dog is also anesthetized with intravenous pentobarbital, intubated, and ventilated with 100 per cent oxygen. The heart and great vessels are exposed through an incision in the left fourth intercostal space. The pleural reflections in the anterior mediastinum are divided with the cautery, and the azygos vein is ligated. Umbilical tapes are passed about the extrapericardial venae cavae avoiding injury to the right phrenic nerve. The pericardial sac is opened longitudinally anterior to the left phrenic nerve, and its edges are sutured to the muscular borders of the incision, thereby excluding lung tissue from the field. Following administration of 2 mg. per kilogram of intravenous heparin, a catheter is placed in the left external jugular vein through a small neck incision, and the tip is passed into the superior vena cava to lie just cephalad to the umbilical tape. The inferior vena cava is similarly cannulated via the left femoral vein. A catheter is placed in the left femoral artery for perfusion and attached to the arterial limb of a rotating disc oxygenator.* A catheter in the right femoral artery allows monitoring of the arterial pressure, and the left femoral vein is catheterized for intravenous infusions.

During total cardiopulmonary bypass, the venae cavae are occluded by the tapes, and venous blood is diverted to a reservoir from which it is pumped to the oxygenator. Arterialized blood is pumped through the femoral artery at a rate averaging 100 ml. per kilogram per minute. The bypass technique is illustrated in Fig. 1.

Removal of the recipient's heart is accomplished in the following manner. A non-crushing clamp is passed through the transverse sinus, and the aorta and pulmonary artery are occluded as far distally as possible within the pericardium. The pulmonary artery is transected distal to the valve commissures, and the aorta is divided about 1 cm. beyond the coronary ostia. The heart is grasped, elevated from the pericardial well, and incised longitudinally along the lateral aspects of both atria. The atrial septum is similarly incised, separating the major portion of the heart from the common posterior atrial wall. The portions of atria which remain in the recipient contain the openings of both venae cavae and the pulmonary veins as well as a ridge of atrial septum (Figs. 2 and 3). During the procedure, bronchial flow is returned to the oxygenator by means of a suction tip in the pericardial well.

At this point the same technique is used for removal of the donor heart following inflow and outflow occlusion. Excision of the heart is completed in

*Kay-Cross Oxygenator, Pemco Inc., Cleveland, Ohio.

approximately 1 minute, and the heart is immediately placed in isotonic saline at 4° C. After 5 minutes the myocardial temperature reaches 12° to 15° C. as measured by a thermistor in the tip of a small gauge hypodermic needle. During this time, the heart blanches, and contractions diminish in frequency eventually becoming imperceptible.

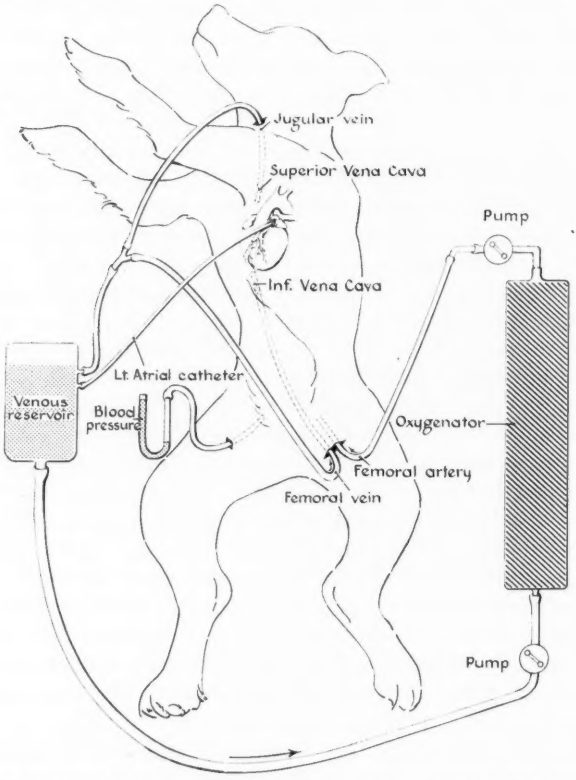


Fig. 1.—The method of cardiopulmonary bypass using a rotating disc oxygenator.

Stay sutures are placed and tied at either end of the atrial septal ridge. This maneuver properly orients the graft, and a simple continuous suture then readily approximates the edges of the donor atria and atrial septum to the atrial walls and septum of the recipient, as seen in Fig. 4. The aorta and pulmonary artery are joined to the corresponding vessels of the recipient by continuous suture. Prior to completion of the aortic suture line, a catheter is inserted through the left atrial appendage into the left ventricle to avoid distention of the heart. Following completion of all anastomoses, coronary circulation is re-established by removing the clamp from the transverse sinus. Total duration of cardiac anoxia is approximately 1 hour.

Coronary air embolism is avoided by allowing bronchial blood to fill the left heart before the last stitch is taken in the aortic anastomosis. As the heart

rewarms during perfusion of the coronary vessels, ventricular fibrillation becomes visible and progressively more vigorous. After 10 minutes of coronary flow, 1 ml. of 1:12,000 epinephrine is injected into the left ventricle followed by gentle intermittent compression and electrical defibrillation. A few minutes prior to defibrillation regular contractions of the atria are usually noted. Support with the heart-lung machine is continued for another 10 minutes during which a slow intravenous drip of 2 mg. of levarterenol in 300 ml. of isotonic

Fig. 2.—A photograph of the pericardial well after removal of the recipient's heart. The common posterior atrial wall remains with the openings of the superior vena cava *(SVC)*, inferior vena cava *(IVC)*, and pulmonary veins *(PV)*. A ridge of atrial septum *(AS)* also remains.

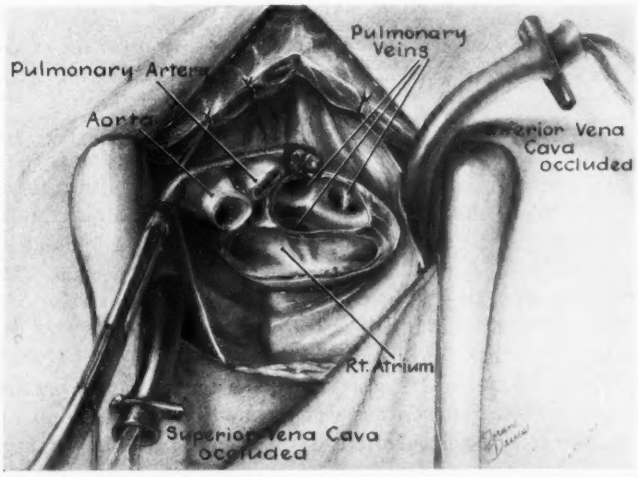


Fig. 3.—An artist's drawing of the area prepared to receive the cardiac homograft. Compare with Fig. 2.

saline is started. The transplanted heart gradually assumes support of the circulation aided by the levarterenol drip. Total duration of cardiopulmonary bypass is usually about 1 hour and 30 minutes. Polybrene, 2.5 mg. per kilogram, is administered slowly, and the cannulae are removed. A siliconized rubber chest tube is inserted, and the incision is closed in layers.

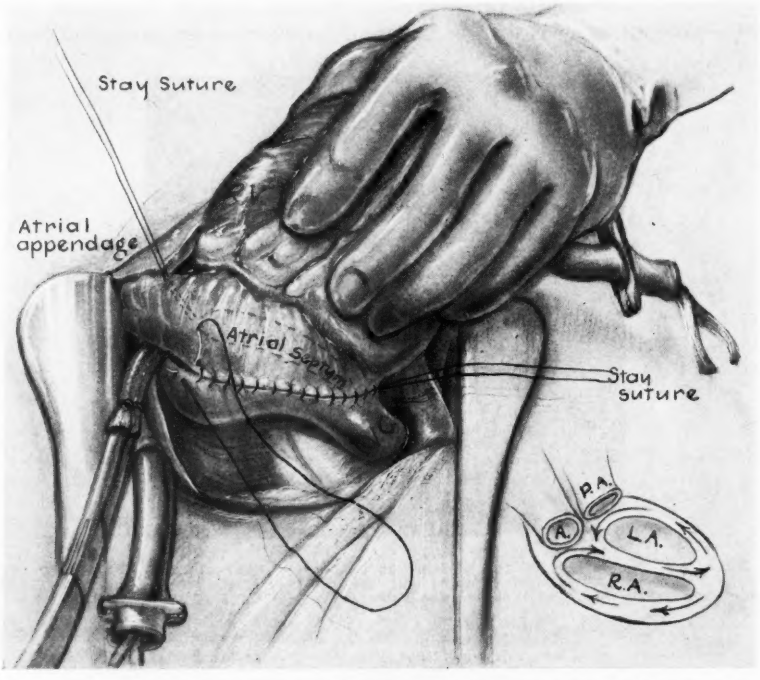


Fig. 4.—Following placement of stay sutures at either end of the atrial septum, a continuous stitch is used to anastomose the edges of the atrial walls and septum to the corresponding edges of the host tissue. Progression of the atrial anastomosis is illustrated by the insert.

RESULTS

The postoperative course and autopsy findings of the dog that survived 8 days will be described in detail. The animal recovered readily from anesthesia, and by the morning of the first postoperative day he was able to walk and eat. The hind limbs were weak, presumably due to the bilateral femoral artery and vein ligation, but by the third day the gait had become normal. The resting pulse varied from 68 to 92 and increased moderately with exercise. Daily electrocardiograms (Fig. 5) initially revealed sinus rhythm, but later tracings resembled a nodal rhythm. Serial S-T segment changes were consistent with pericarditis. Premature ventricular contractions were never present on any of the tracings. Convalescence was complicated by a wound infection which appeared on the fourth postoperative day. The dog seemed lethargic on the seventh and eighth days, and because of persistent infection, the animal was sacrificed 8 days and 2 hours following the transplantation.

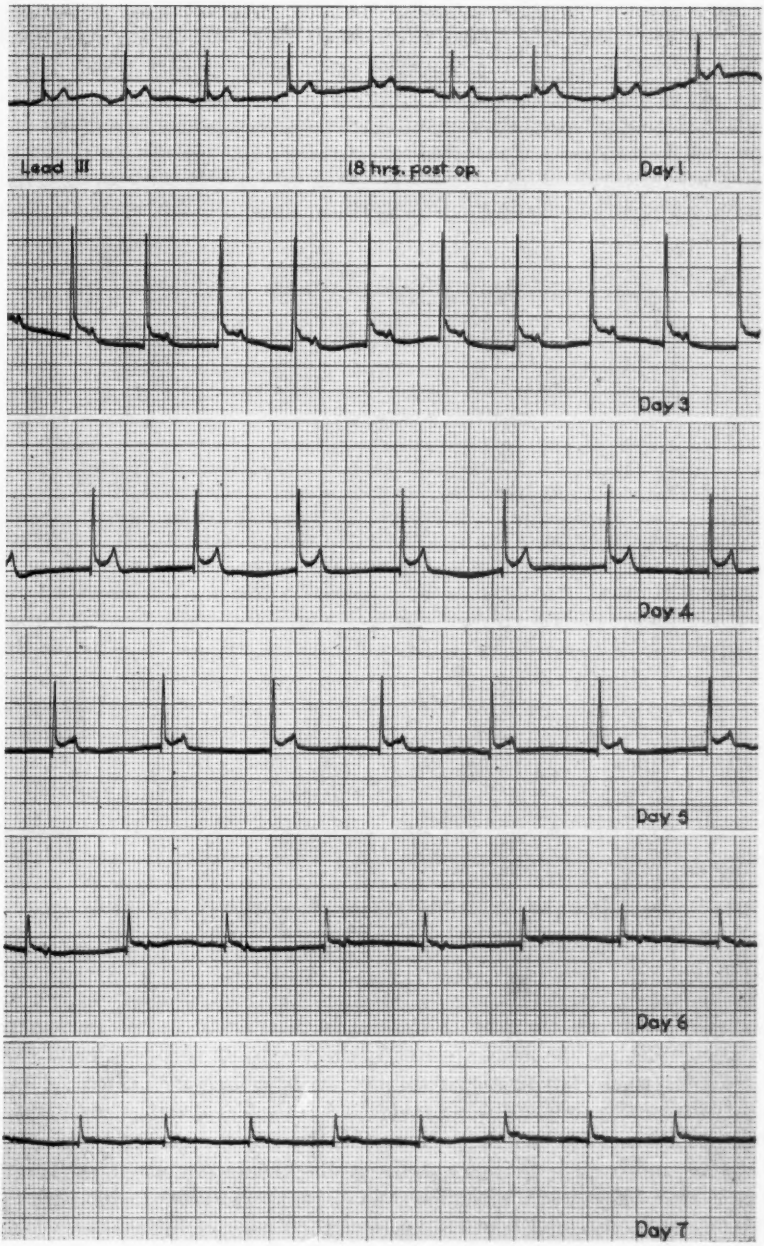


Fig. 5.—The serial ST-T wave changes are compatible with pericarditis. The first tracing contains P waves which are absent in later records.

LIBRARY
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Intravenous Pentothal was administered, and the trachea was intubated for ventilation while the right thorax was opened. There was a moderate amount of fluid in the chest as well as scattered patches of atelectasis. The heart exhibited a regular sinus rhythm at a rate of 72 beats per minute. The right atrium and ventricle were somewhat dilated, and there was a suggestion of tricuspid insufficiency. An electrocardiogram taken from the surface of the right atrium demonstrated the presence of P waves with a P-R interval of 0.14 sec. (Fig. 6). The atrial suture line was examined in situ, and a complete autopsy

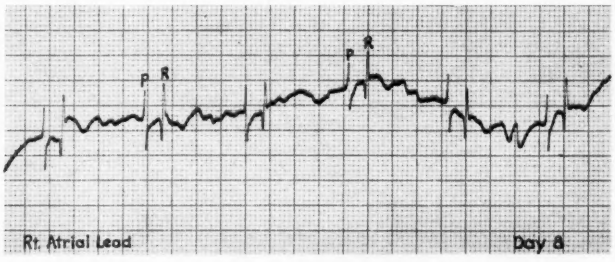


Fig. 6.—An electrocardiogram taken from the surface of the right atrium immediately before sacrificing the animal on the eighth postoperative day. There is sinus rhythm with a P-R interval of 0.14 sec.

was then performed. Aside from the pulmonary complications previously mentioned, significant postmortem findings were confined to the heart. A thrombus partially occluded the superior vena caval-right atrial junction. The remainder of the heart appeared grossly normal except for moderate dilatation of the right heart chambers. At the atrial suture line, donor and recipient tissues were grossly indistinguishable. The ventricular myocardium showed no evidence of infarction. Microscopic sections of the heart revealed a severe, generalized interstitial myocarditis characterized by extensive round cell infiltration with minute areas of cellular necrosis (Fig. 7).

DISCUSSION

The technique which we have described makes it possible to study the cardiac homograft in its normal anatomic position as it performs the work of maintaining the circulation. The need for several venous anastomoses is obviated by leaving intact the posterior walls of the atria. Heparinization of the donor animal prevents the clotting of blood in the coronary vessels during transplantation. Cooling the heart apparently diminishes its metabolic requirements to the point where satisfactory recovery can be anticipated after 1 hour of anoxia. Coronary air embolism is avoided by displacing all air from the left heart with bronchial flow before completing the aortic anastomosis.

Carrel and Guthrie[1, 2] apparently were the first to perform transplantation of the heart. They described implantation of a puppy heart in the neck of an adult dog with re-establishment of coronary circulation by anastomosing the carotid artery of the host to the aorta of the homograft. An hour after operation, rhythmic contractions of the ventricles were observed; in 2 hours the experiment was terminated. Other investigators[3-11] have subsequently performed

similar experiments. Several of the technical problems of transplantation have been delineated—surgical speed to minimize the duration of cardiac anoxia, avoidance of cardiac dilatation, and prevention of intravascular clotting and air embolism.

Marcus and his associates[5] first suggested that a cardiac homograft might conceivably support the circulation of the host, but this was considered, ". . . a matter of fantastic speculation for the future." They[6] suggested further that a homologous heart transplant might partially support the circulation during open-heart surgery.

Fig. 7.—A photomicrograph of the myocardium showing round cell infiltration with some cellular necrosis.

Neptune and his associates[12] attempted complete replacement of the canine heart and lungs by homologous transplantation. They used moderately deep hypothermia of 21° to 25° C. Maximal survival was 6 hours. Blanco and co-workers[13] transplanted the heart and lungs of the dog using a pump-oxygenator and potassium arrest with survival to 4½ hours. Webb and co-workers[14, 15] recently reported their experiences with a technique for transplanting the heart and right lung. Prior to insertion in the recipient animal, the donor tissue was refrigerated in cold Tyrode's solution. Maximal survival was 7½ hours, but cardiac action was vigorous.

Our experience illustrates that a denervated cardiac homograft in the dog will adequately support the circulation for several days. The microscopic picture of an interstitial myocarditis is indistinguishable from that which characterizes many hypersensitivity states. Presumably, in this instance, it represents the process of homograft rejection by the host.

SUMMARY

A technique is presented for the homovital transplantation of the canine heart. The main features of the method include: (1) refrigeration of the heart in cold saline to diminish its metabolic requirements during the anoxic period, (2) preservation of the posterior atrial walls of the recipient to avoid several venous anastomoses, and (3) maintenance of the recipient animal's circulation with the pump-oxygenator until the graft is fully able to resume its function.

This technique has resulted in survival for 8 days with complete support of the circulation by the denervated transplanted heart.

ADDENDUM

Subsequent cardiac transplantations have resulted in survival of the recipient animals for periods up to 21 days. Prior to the terminal rapid downhill course the animals display normal activity and exercise tolerance, illustrating the remarkably normal function of the denervated transplanted heart.

REFERENCES

1. Carrel, A., and Guthrie, C. C.: The Transplantation of Veins and Organs, Am. Med. **10**: 1101, 1905.
2. Carrel, A.: The Surgery of Blood Vessels, Bull. Johns Hopkins Hosp. **18**: 18, 1907.
3. Mann, F. C., Priestley, J. T., Markowitz, J., and Yater, W. M.: Transplantation of the Intact Mammalian Heart, Arch. Surg. **26**: 219, 1933.
4. Sinitsin, N. P.: A Transplantation of the Heart (Russian Text.), Klin. Med. (Mosk.) **31**: 5, 1953.
5. Marcus, E., Wong, S. N. T., and Luisada, A. A.: Homologous Heart Grafts: Transplantation of the Heart in Dogs, S. Forum **2**: 212, 1951.
6. Marcus, E., Wong, S. N. T., Luisada, A. A., and Liu, W. C.: Homologous Heart Grafts. I. Technic of Interim Parabiotic Perfusion. II. Transplantation of the Heart in Dogs, A. M. A. Arch. Surg. **66**: 179, 1953.
7. Luisada, A. A., and Marcus, E.: The Behavior of a Transplanted Heart, Cardiologia **25**: 197, 1954.
8. Downie, H. G.: Homotransplantation of the Dog Heart, A. M. A. Arch. Surg. **66**: 624, 1953.
9. Wesolowski, S. A., and Fennessey, J. F.: Pattern of Failure of the Homografted Canine Heart, Circulation **8**: 750, 1953.
10. Sayegh, S. F., Creech, O., Jr., and Harding, J. H.: Transplantation of the Homologous Heart, S. Forum **8**: 317, 1957.
11. Sayegh, S. F., and Creech, O., Jr.: Transplantation of the Homologous Canine Heart, J. THORACIC SURG. **34**: 692, 1957.
12. Neptune, W. B., Cookson, B. A., Bailey, C. P., Appler, R., and Rajkowski, F.: Complete Homologous Heart Transplantation, A. M. A. Arch. Surg. **66**: 174, 1953.
13. Blanco, G., Adam, A., Rodriguez-Perez, D., and Fernandez, A.: Complete Homotransplantation of Canine Heart and Lungs, A. M. A. Arch Surg. **76**: 20, 1958.
14. Webb, W. R., and Howard, H. S.: Cardio-pulmonary Transplantation, S. Forum **8**: 313, 1957.
15. Webb, W. R., Howard, H. S., and Neely, W. A.: Practical Methods of Homologous Cardiac Transplantation, J. THORACIC SURG. **37**: 361, 1959.

EXTRACORPOREAL CIRCULATION IN CARDIAC SURGERY

Report on First 50 Cases

E. J. Zerbini, M.D., F.A.C.S., Adib D. Jatene, M.D., Radi Macruz, M.D., Nagib Curi, M.D., and Geraldo Verginelli, M.D., São Paulo, Brazil

From July, 1958, to July, 1959, we operated upon 50 patients with cardiovascular lesions, using a pump-oxygenator for cardiopulmonary bypass. The pump was occlusive and of a modified De Bakey type, the oxygenator a Kay-Cross, and the intracardiac suction system similar to the one used by Lillehei.[1] No filters were used except for the donor blood introduced.

Our present series could be divided in two groups (Fig. 1). In the first one, 22 patients operated upon during the period between July, 1958, and February, 1959, the mortality rate was very high (45.45 per cent). This rate dropped to 15.37 per cent in the second group (March, 1959—July, 1959).

GROUP 1

The high mortality in the first group was due in part to the inclusion of patients with far-advanced stages of their disease, and in part to errors which were not repeated later. The following defects were represented in the 10 patients who did not survive.

CASE 1.—A. V. *Pulmonary infundibular stenosis with an intact interventricular septum.* The bypass lasted 50 minutes; no precautions were taken to prevent flooding of the lungs with blood and distention of the heart during and shortly after induced cardiac arrest. The patient died 2 days postoperatively from pulmonary complications. We now realize the dangers of prolonged cardiac arrest using acetylcholine or potassium citrate, especially in very hypertrophied hearts. We also realize that there is no need whatsoever for cardiac arrest in order to correct completely an infundibular stenosis. As a matter of fact, a beating heart gives a much better idea of how much and where to resect.

CASE 2.—A. C. *Pulmonary valvular stenosis with an interatrial septal defect.* The patient died on the fifth postoperative day. Postmortem examination revealed a hemothorax and pulmonary atelectasis. Even though the patient had had a bilateral thoracotomy, this certainly should have been a preventable death.

CASE 3.—I. A. *Interventricular septal defect with pulmonary hypertension.* The defect was quite small and was closed without the use of any patch. Relative to this point,

From the Department of Surgery of the University of São Paulo Medical School, São Paulo, Brasil. (Prof. A. Corrêa Netto.)

Read at the commemorative Session of the Centenary of the Sociedade Portugueza de Beneficência at Santos, Brazil, Aug. 20, 1959.

Received for publication Dec. 26, 1959.

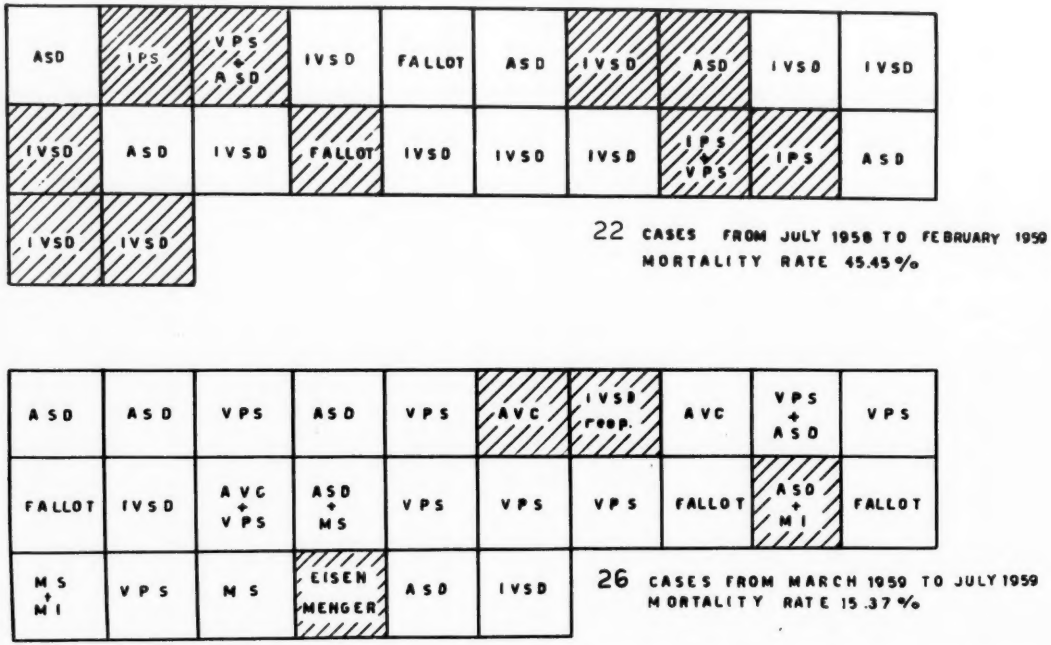


Fig. 1.—Mortality rate of our first 48 cases of total extracorporeal circulation. ASD—atrial septal defect; IPS—infundibular pulmonic stenosis; VPS—valvular pulmonic stenosis; IVSD—interventricular septal defect; Fallot—tetralogy of Fallot; AVC—atrial ventricular canal; MS—mitral stenosis; MI—mitral insufficiency.

we came to the conclusion that it is far safer to use a patch in every ventricular septal defect, irrespective of its size, as we had the sad experience of reoperating upon 2 patients with very small defects closed at first by sutures only. The first one showed signs of re-opening of the defect in the immediate postoperative course while the second was fortunate in that he gave evidence of re-opening of the defect just before the ventriculotomy was closed and shortly after the arrested heart resumed its normal beating. The patient I. A. died 24 hours postoperatively possibly from an A-V block that might have developed shortly before death.

CASE 4.—B. F. *Interatrial septal defect.* The perfusion was poorly controlled and a sudden fall of the blood level in the Kay-Cross oxygenator produced foam, a large amount of which was pumped into the patient who died in cerebral coma on the fourth postoperative day.

CASE 5.—C. V. M. *Interventricular septal defect with pulmonary hypertension.* A persistent ductus arteriosus which was overlooked caused severe pulmonary complications which led to death of the patient on the second postoperative day.

CASE 6.—A. O. A. *Tetralogy of Fallot.* A-V block required the reopening of the median sternotomy in order to insert a wire for the pacemaker; this was easily and rapidly performed. Unfortunately the patient vomited a large volume of gastric content which was aspirated into his lungs, thus producing asphyxia and death.

CASE 7.—S. M. M. *Pulmonary infundibular and valvular stenosis with a very narrow pulmonary valve ring.* Forty minutes of cardiac arrest without the recommended measures to prevent flooding of the lungs and distention of the heart. The patient died in heart failure and severe pulmonary complication 2 days after the operation.

CASE 8.—L. E. P. *Pulmonary infundibular stenosis.* Thirty minutes of cardiac arrest. This patient died on the third postoperative day in heart failure. This case taught us that ventriculotomy without thorough and total relief of the infundibular stenosis could be fatal. This also happened in Case 7.

CASE 9.—F. S. N. *Interventricular septal defect with pulmonary hypertension.* Fifty minutes of cardiac arrest without the recommended measures to prevent flooding of the lungs and distention of the heart. The patient died 3 days later from severe pulmonary damage.

CASE 10.—A. G. *Interventricular septal defect with pulmonary hypertension.* The patient died 4 hours later from severe pulmonary damage.

DISCUSSION

Cardiac surgery with extracorporeal circulation presents many problems that are not met with in the usual surgical procedures, as, for example, the hemorrhagic syndrome produced by heparin. Open-heart surgery would be much safer and more widespread if an ideal anticoagulant were found to replace heparin or else a true neutralizer to counteract all its effects was found. Until then the only weapon we have to prevent serious bleeding complications is to perform a thorough and complete surgical hemostasis by electrocoagulation of every tiny blood vessel, even capillaries, that might be oozing. We are also inclined to believe that many of the pulmonary complications may also be related to heparin. The lungs gradually show a diffuse interstitial bleeding and the patients die from severe respiratory insufficiency in spite of all attempts to improve ventilation artificially. Finally, at the autopsy table blood is found

flooding the bronchial tree, leaving no air whatsoever in either lung. Minor degrees of this unusual condition were noticed in a few other patients who survived. This probably explains the atelectasis which does not follow the bronchial tree distribution as noticed by Dodrill.[2] The atelectasis is produced by compression from regional bleeding. This complication is most common in diseases that present severe pulmonary hypertension. We have not seen this type of complication in severe hypertension secondary to patent ductus arteriosus for which surgery is done without heparin. As a matter of fact, in our experience in chest surgery, the pulmonary complications are different from those seen after extracorporeal circulation. In order to improve our clinical results following the first group of patients in our present series we put into practice the following measures:

1. *During the surgical procedure:* (1) Median sternotomy whenever feasible; nonopening of the pleural spaces if possible. (2) In bilateral thoracotomy, manipulation of the lungs should be very gentle and minimal; drying should be minimized by humidification. (3) Drainage of the left atrium during cardiac arrest when operating on interventricular septal defects, tetrads, and when the interventricular and interatrial septum are intact. (4) Routine search for a patent ductus arteriosus which should be closed. (5) Complete relief of valvular and/or infundibular stenosis when a ventriculotomy is performed. (6) Immediate use of a pacemaker as soon as an A-V block is noticed.

2. *Pulmonary ventilation:* During the perfusion the lungs are kept partially inflated with 100 per cent O_2, maintaining a mean endotracheal pressure of approximately 8 cm. of water.

3. *In the postoperative period:* (1) Precise control of the blood volume. (2) Prevention of pulmonary complications by the use of a tracheostomy when necessary; this permits secretions to be easily removed and artificial respiration to be instituted if necessary. (3) Treatment of heart failure and the use of vasodilators for pulmonary hypertension.

GROUP 2

As mentioned before, our mortality rate dropped to 15.37 per cent after we adopted the aforementioned measures in the second group of patients in our series. It is important to emphasize that the cases were very similar to the ones in the first series and, in some, the patients were in just the same poor condition because of the far-advanced stage of their disease. The four deaths in this second group will be briefly analyzed.

CASE 1.—R. P. A. *Persistent atrioventricular canal (partial form).* Hemolysis was quite high at the end of perfusion and a prolonged systemic hypotension developed. The patient died on the seventh postoperative day from a renal shutdown.

CASE 2.—I. N. A. *Reoperation of a reopened interventricular septal defect which was closed by simple sutures.* Bacterial endocarditis was also one of the complications of the first operation. The patient died shortly after the second operation; the heart action was very feeble after cardiac arrest and could not take over when the extracorporeal circulation was stopped.

Case 3.—I. M. *Interatrial septal defect with mitral valve stenosis and insufficiency.* The patient died 3 days later from severe pulmonary damage.

CASE 4.—*Eisenmenger complex with clinical cyanosis for the previous 6 years.* We believe this to be the first reported case of this type in which there was surgical correction. Because of the accepted concept that no surgery should be performed on such patients, we had an indwelling catheter in the right ventricle during a long period of observation; venous pressure was also monitored. As no significant changes were noted and as the heart even showed a better aspect than before closure of the large defect, we closed the chest incision.

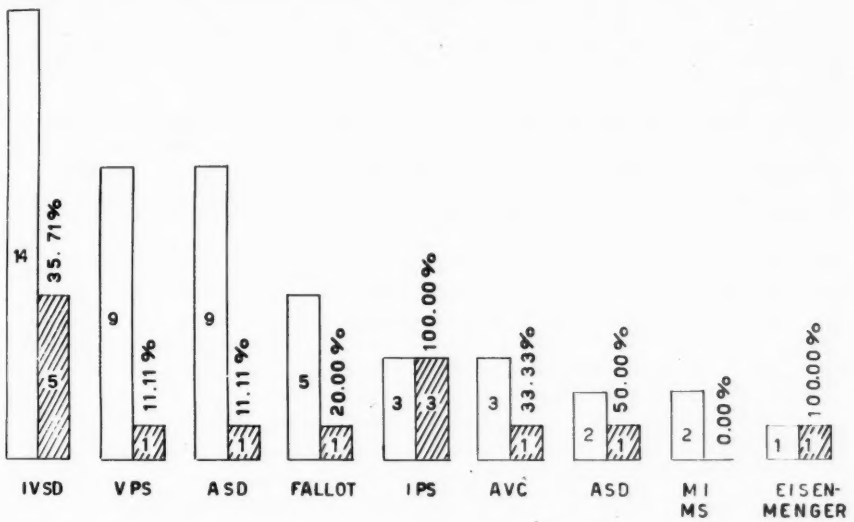


Fig. 2.—Results of our first 48 cases of total extracorporeal circulation. IVSD—interventricular septal defect; VPS—valvular pulmonic stenosis; Fallot—tetralogy of Fallot; IPS—infundibular pulmonic stenosis; ASD—atrial septal defect; AVC—atrial ventricular canal; MI—mitral insufficiency; MS—mitral stenosis.

The patient died shortly after she was moved to the recovery room. The death was definitely by asphyxia. A progressive cyanosis developed in spite of oxygen, and the patient stopped breathing. The chest incision was promptly reopened; the heart was still beating although weakly. Cardiac massage was of no avail as the lungs had total atelectasis that did not respond to endotracheal artificial respiration because of widespread pulmonary bleeding. The lungs in this case were very similar to those in the case previously described; they looked almost like a congested liver.

Fig. 2 presents the same series with the cases grouped according to the different diseases.

1. *Interventricular septal defects* (14). Six of the patients had cyanosis on effort and, with exception of 1 case, the pulmonary artery pressures were over 70 per cent of the systemic pressures. They were all operated upon by way of a median sternotomy; the bypass lasted from 26 to 105 minutes, cardiac arrest from 8 to 56 minutes, the flow rate from 75 to 150 c.c. per kilogram per minute. Five patients had their defects closed by simple sutures while the other 9 had an Ivalon patch (1 to 2.5 cm. in diameter) sutured to the defect, using interrupted silk sutures. There were 5 deaths in this group (37.71 per cent).

2. *Pulmonary valvular stenosis* (9). Six patients were operated upon using a bilateral thoracotomy and 3, a median sternotomy. The duration of the bypass varied between 18 and 60 minutes. Two patients had a combined interatrial septal defects which were also closed. Only 1 patient in this group did not survive.

3. *Interatrial septal defects with slight to severe pulmonary hypertension* (9). One patient had an associated anomalous pulmonary venous drainage of the right superior vein into the superior vena cava. The bypass time varied from 15 to 96 minutes; the flow rate varied from 55 to 100 c.c. per kilogram per minute. We had only one death in this group.

4. *Tetralogy of Fallot* (5). One of the patients had been previously subjected to two Blalock operations. The red blood cell count varied from 4 to 10 million in these patients; they were all cyanotic. Three underwent infundibular resection and pulmonary valvulotomy; 2 had only infundibular resections. The interventricular septal defect was closed by an Ivalon patch and the outflow tract was enlarged by the use of an Ivalon-Teflon patch. Only 1 patient died.

5. *Pulmonary infundibular stenosis* (3). Resection of the infundibulum was done in 1 patient an associated interatrial septal defect was closed and pulmonary valvotomy was performed. The third patient had a very narrow pulmonary valve ring which was resected; the pulmonary artery was reimplanted in the right ventricle. The bypass lasted 50, 111, and 151 minutes and the cardiac arrest period was 15, 35, and 36 minutes. The 3 patients died.

6. *Atrial ventricular canal* (3). Two were partial and the third complete and with an associated pulmonary stenosis. In this last patient, the bypass lasted 140 minutes without any complications whatsoever. The lesion was completely corrected. There was one death.

7. *Interatrial septal defects with mitral valve disease* (2). One patient had mitral stenosis (Lutembacher syndrome), the correction was very satisfactory and the patient is alive. The other patient had mitral insufficiency also which was corrected by an Ivalon prosthesis. This patient died 3 days later.

8. *Mitral valve lesions* (2). The first patient had a re-stenosis after a previous mitral commissurotomy; while the second had insufficiency also. Both lesions were completely corrected under direct vision. Both patients are well.

9. *Eisenmenger complex* (1). The patient died from pulmonary hemorrhage.

10. *Large aortic aneurysms* (2). As these aneurysms were of the descending aorta, only partial bypass from left atrium to femoral artery was used. They were both successfully resected and replaced by alcohol-preserved homografts. One patient was operated upon as an emergency procedure while dying from asphyxia; he is doing very well now, about 6 months postoperatively. The second one died on the twenty-first postoperative day from rupture of the graft at the site of an intercostal branch which had atherosclerotic changes at its origin from the aorta.

CONCLUSIONS

Fifty patients suffering from different congenital and acquired cardiovascular diseases were operated upon with the use of pump-oxygenator. Two patients with aortic aneurysms were operated upon with a partial bypass. In the first 22 cases of total extracorporeal circulation, the mortality was 45.45 per cent; the main cause of death was pulmonary damage (5 cases). The other patients died from hemothorax, possible heart block, cerebral embolism, aspiration of vomitus, and heart failure.

Many prophylactic measures were taken and the mortality in the last 26 patients dropped to 15.37 per cent. In this group, the cause of death was renal shutdown in 1, heart failure and pulmonary complications in the others.

ADDENDUM

Since this article was submitted for publication, the authors' experience has been enlarged by 107 cases, as follows: 23 cases of interventricular septal defect (7 deaths); 23 cases of tetralogy of Fallot (7 deaths); 17 cases of atrial septal defect, 4 of which were associated with anomalous pulmonary venous drainage (1 death); 11 cases of valvular pulmonic stenosis (no death); 4 cases of valvular pulmonic stenosis plus atrial septal defect (1 death); 4 cases of infundibular pulmonic stenosis (3 deaths); 5 cases of atrial ventricular canal (2 deaths); 10 cases of mitral lesions (3 deaths); 6 cases of aortic stenosis (no death); 1 Eisenmenger complex (1 death); 1 case of nonsurgical lesion (no death); 2 cases of aortic aneurysms (1 death).

REFERENCES

1. Lillehei, C. W., and DeWall, R. A.: Design and Clinical Application of the Helix Reservoir Pump-Oxygenator System for Extra-corporeal Circulation, Postgrad. Med. 23: 561-573, 1958.
2. Dodrill, F. D.: The Effects of Total Body Perfusion Upon the Lungs *in* Extracorporeal Circulation, edited by J. Garrott Allen, Springfield, Ill., 1958, Charles C Thomas, publisher, p. 332.

EXPERIMENTAL CIRCULATORY ARREST AND ELECTRICAL ACTIVITY OF THE BRAIN

A. A. Lepore, M.D., and F. Morin, M.D., Detroit, Mich.*

THE EMPLOYMENT of hypothermia for cardiac surgery has prompted the study of brain activity during cooling and rewarming. The general results of previous studies indicate that with the lowering of the body temperature the electrical cortical activity decreases in frequency and amplitude and virtually disappears when the temperature is as low as 20° C. With rewarming, the activity returns progressively to control levels.[4, 5, 10, 16]

In treatment of some cardiac defects, a total arrest of the circulation for relatively long periods of time is sometimes necessary. The available clinical evidence suggests that interruption of circulation beyond 8 minutes is dangerous for the survival of the central nervous system in man. How long the central nervous system of a homothermic animal can tolerate a circulatory arrest during hypothermia is not clearly established.

In previous experimental studies, the circulatory arrest was either maintained for short periods of time[10] or was not achieved because the azygos vein was left untied. The importance of the azygos flow in maintaining adequate blood supply to the central nervous system in normothermic animals during vena caval occlusion was clearly shown by Andreasen and Watson[1] and by Cohen and Lillehei.[7] General systemic effects of hypothermia and circulatory arrest have been carefully analyzed.[2, 3, 15] How these systemic effects are reflected in the electrical activity of the brain is not known. It is also not known to what extent the recovery of the electrical activity of the brain in animals, cooled and subjected to circulatory arrest, parallels the events occurring in cooled animals not subjected to the circulatory arrest. It was considered that animal experiments involving arrest of the circulation during hypothermia would supply some useful information on these various aspects of the problem.

MATERIALS AND METHODS

Twenty-two experiments on 18 cats and 1 monkey were performed under sodium pentobarbital anesthesia (30 mg. per kilogram, intraperitoneally). The electroencephalogram (EEG) was recorded with a six-channel inkwriter using stainless steel screws in contact with the dura.

From the Wayne State University College of Medicine, Detroit, Mich.
Supported by U. S. Public Health Service Grant B 405 C.
Received for publication Jan. 6, 1960.

*Formerly Fellow of the Michigan Heart Association, Henry Ford Hospital, Detroit, Mich., and Resident in Cardiovascular Surgery, St. Francis Hospital and Sanatorium, Roslyn, N. Y. This work was done while a Research Fellow at the Henry Ford Hospital.

Needle electrodes, insulated but for the tip, were introduced by means of a stereotaxic apparatus. The position of the surface as well as the deep electrodes were controlled at the end of the experiment. The electrodes on the surface were placed so as to survey the main cortical areas of both hemispheres. These areas included routinely the occipital and parietal regions.

A tracheal cannula was inserted. The chest was entered through the fourth intercostal space and artificial respiration was started at 24 cycles per minute (room air). Superior and inferior venae cavae and the azygos vein were prepared by passing umbilical tape around each vein. In two experiments (1 cat, 1 monkey), the aorta and the pulmonary artery were also prepared for clamping. This was done while the animal was anesthetized and before the beginning of cooling. Cooling was achieved by placing chilled water and ice cubes around the body. When the desired temperature was reached, the veins were occluded. In all experiments, paralyzing doses of d-tubocurarine, from 0.5 to 1.0 mg. per 10 pounds of body weight, were injected intravenously to prevent shivering. Additional general anesthesia was avoided; temperature was measured by a rectal thermometer. The time required for decreasing the body temperature to 20° to 25° C. varied between 1 and 2 hours. Rewarming was achieved by application of hot water bottles and irradiation with an infrared lamp.

As a consequence of hypothermia, or cardiac manipulation, fibrillation occurred in several cases. Defibrillation was accomplished by applying a 50-cycle 120-volt current to the heart for periods of 3 to 5 seconds. Generally only one electric shock was necessary but, in a few instances, it had to be repeated three or four times. In the monkey, ventricular fibrillation occurred when the body temperature was 20° C. and complete cardiac arrest was induced by an injection of potassium chloride (5 per cent, 1 c.c. per kilogram) in the left ventricle (according to Lam's method[12, 13]). Resuscitation was effected by intermittent cardiac compression and defibrillation shocks.

RESULTS

1. *Effects on EEG by occluding the venae cavae only or in combination with azygos vein at normal body temperature.*

The effects of such a procedure are illustrated in Fig. 1. Following clamping of both venae cavae, the cortical activity changes after a delay of 3 to 6 seconds. These changes consist mainly in a considerable decrease in amplitude of the records and in alternating spindling and quiescent periods. Such changes occur in the surface as well as in the deep leads (Fig. 1, *B, C, D*). The return to the control pattern is very brisk and follows almost immediately the release of the clamps (Fig. 1, *E*). If both venae cavae are kept closed for as long as 3 minutes the records become very reduced in amplitude and show some diminution of higher frequency components. The return to normal in this case is somewhat delayed (20 to 26 seconds). It appears evident that the cortical activity continues after the closure of the caval veins but with rather marked changes with respect to control record.

When the azygos vein is also clamped simultaneously with the venae cavae, the EEG activity disappears within 4 to 7 seconds after the closure and

remains flat throughout (3 minutes) (Fig. 2, *A-D*). The return to normal is much slowed down and the first evidence of activity is apparent 1 minute after release of the clamps and improves slowly throughout the successive 2 to 3 minutes (Fig. 2, *E-G*). In this case the deep records returned toward the normal level before the surface leads. Tracings comparable to the control were present approximately 5 to 10 minutes after the reopening of the 3 veins (Figs. 2-4).

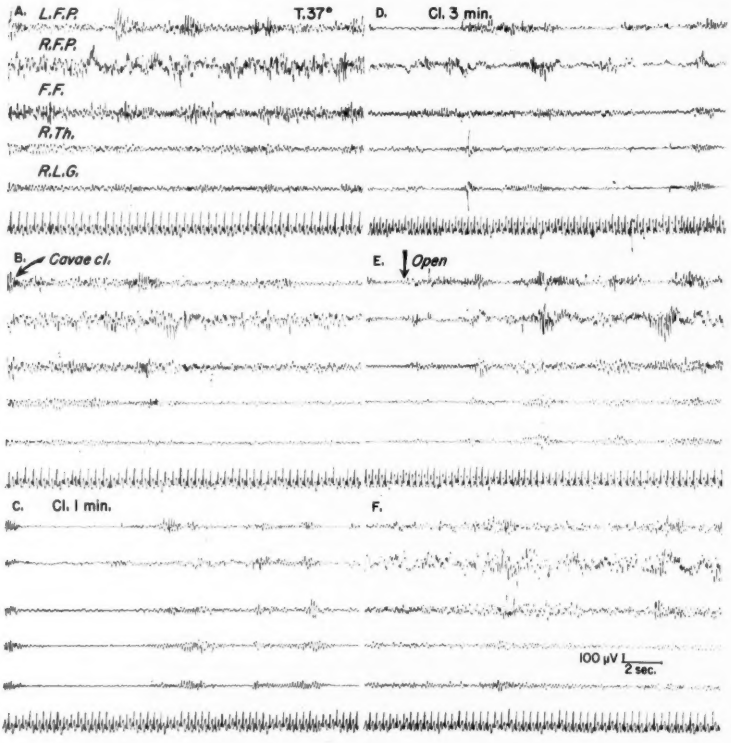


Fig. 1.—EEG changes produced by occlusion of venae cavae (azygos open) at normal temperature (37° C.).

A, Control. *B*, The caval veins are clamped; at *arrow*. *C*, One minute. *D*, Three minutes after occlusion; at *arrow* in *E*, clamps are released. *E*, Continuous record. *F*, Continuous record.

L. F. P. Left frontoparietal cortex. *R. F. P.* Right frontoparietal cortex. *F. F.* Bifrontal. *R. Th.* Right thalamus (cap. nuclei). *R. L. G.* Right lateral geniculate body.

In other experiments, the 3 veins were kept closed for a shorter time (2 minutes). The disappearance of activity of the EEG was always abrupt but recovery was considerably faster.

2. *Closure of caval and azygos veins in hypothermia.* The three veins were closed for 10 minutes at 23° C. in 2 animals.

The changes during cooling are shown in records *A* through *D* of Fig. 3. Slowing of the records and diminution of higher frequency components is a

characteristic feature of cooling as described by other authors. Every trace of activity disappears after the closure (Fig. 3, *E*).

The cortical and subcortical leads show a fast low record after rewarming. The activity as seen in Fig. 3 is similar to that in record *A* but somewhat reduced in amplitude. Some high voltage discharge, initially present in the deep leads, did not reappear. The return toward the normal pattern proceeds slowly and begins about 5 minutes after reopening of the 3 veins (Fig. 3, *G*). Low voltage 1 per second deflections are recognizable in *G* in two leads. The frequency increases in *H* and the record assumes a fairly normal appearance in *I* at 28° C. 1 hour after the reopening of the three veins.

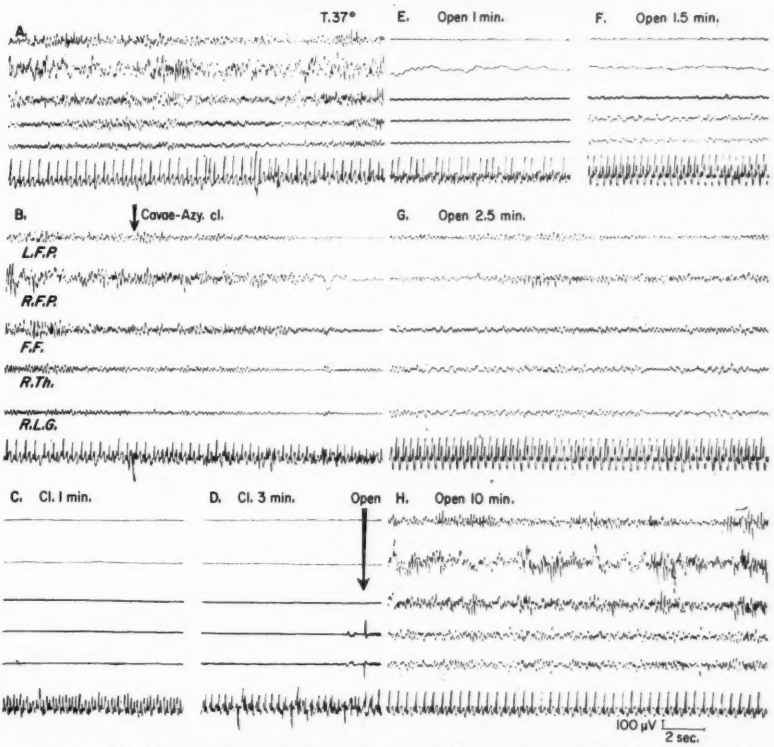


Fig. 2.—EEG changes following occlusion of caval and azygos veins at normal temperature. Veins clamped at arrow *B*; *C*, one minute; *D*, 3 minutes after occlusions. *E*, *F*, *G*, *H*—1, 1.5, 2.5, and 10 minutes, respectively, after releasing of clamps. (Leads same as in Fig. 1.)

In another experiment, the three veins were closed for 15 minutes at 23° C. Two of the cortical leads were placed on the auditory areas, and showed the evoked potentials produced by clicks; such evoked potentials were present at 25° C., and even 23° C. This is an interesting finding because it indicates that some neuronal systems are functioning in a normal way at such low temperature. The presence of auditory-evoked potentials after rewarming also is proof that the cortical elements concerned with sound perception are functionally normal.

The three veins were kept closed for 20 minutes (temperature, 23° C.) in eight experiments, and in 6 of these a similar course of events occurred, as the one described, for the animals with venous return occluded for 10 and 15 minutes.

In Fig. 4 a considerable amount of activity was present at 22° C. in all leads (Fig. 4, *D*) and was suddenly abolished by clamping the veins (Fig. 4, *E*).

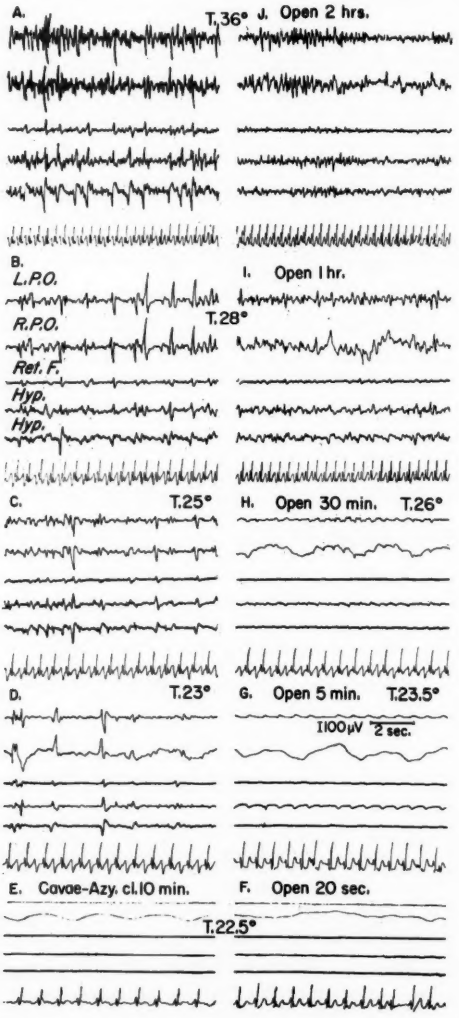


Fig. 3.—Veins occluded for 10 minutes at a temperature of 23° C. Notice synchronous spike discharges in all leads, evident at 25° and 23° C. during cooling *(C, D,)*, absent following recovery from occlusion *(G to H)*. All areas are similarly affected, and recovery is delayed for all.

L. P. O., Left parieto-occipital. *R. P. O.*, Right parieto-occipital. *Ret. F.*, Reticular formation of the midbrain. *Hyp.*, Hypothalamic leads.

As in other cases, the recovery of the electrical activity was slow and did not return to the initial level. Again, here the presence of auditory-evoked potentials gave a clear indication that cortical neurons were capable of normal functions regardless of obvious differences in pattern of activity between the initial and final stages of the experiment (Fig. 4, *H*).

In only 2 out of 8 animals in which the veins were clamped for 20 minutes did the EEG not return to normal.

One experiment was carried out in a monkey. The venae cavae and the aorta and pulmonary artery were clamped for 20 minutes at 20° C. Fibrillation

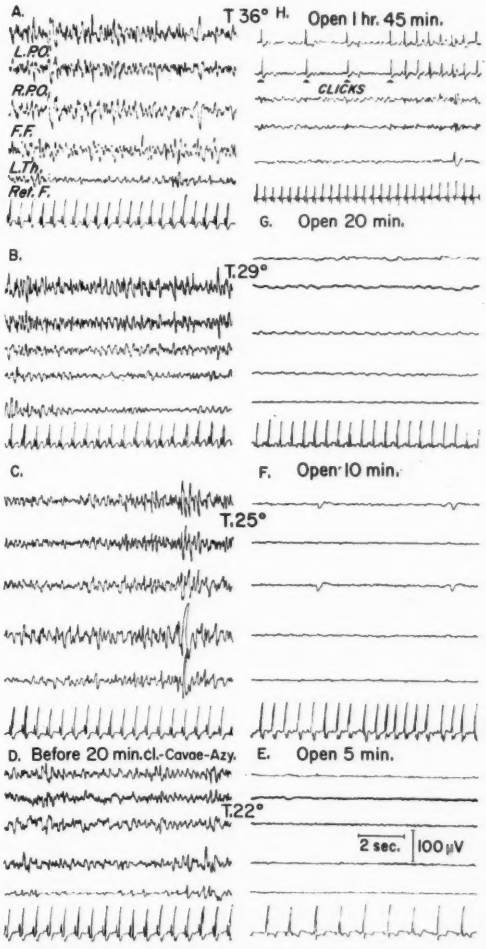


Fig. 4.—In this experiment, considerable activity was present at temperature 22° C. in all leads. Notice delayed return following vein occlusion for 20 minutes. In *H*, auditory potentials in both cortical leads, while spontaneous activity is greatly reduced.

L. P. O., Left parieto-occipital. *R. P. O.*, Right parieto-occipital. *F. F.*, Bifrontal. *L. Th.*, Left thalamus. *Ret. F.*, Reticular formation of midbrain.

occurred and cardiac arrest was produced by injecting potassium chloride, 5 per cent, in the left ventricle. By intermittent compression, the heart was resuscitated and returned to normal rate with rewarming.

Three of the four cortical leads showed little or no activity at the end of the rewarming period.

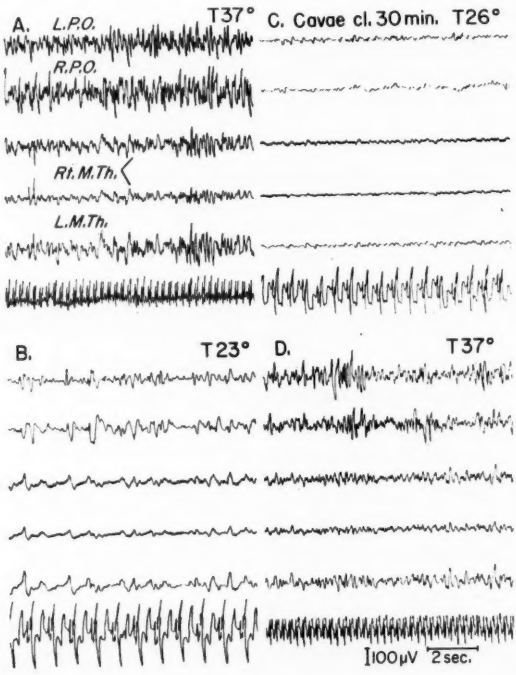


Fig. 5.—The venae cavae were occluded for 30 minutes, azygos left open. Observe the amount of activity present at 23° C. before the occlusion, *B*. *C*, Low amplitude. Activity still present immediately before opening. *D*, Return to normal levels.

L. P. O., Left parieto-occipital. *R. P. O.*, Right parieto-occipital. *Rt. M. Th.*, Medial thalamus of the right side. *L. M. Th.*, Medial thalamus of the left side.

3. *Occlusion of the venae cavae with azygos vein open.* In 5 cats the caval veins were occluded; in 2 cases for 20 minutes, in 1 for 26, and in 3 for 30 minutes.

In an experiment in which both venae cavae were occluded and the azygos left open for 20 minutes at a body temperature of 23° C., it was observed at 31° C. during rewarming that the cortical pattern was similar to that of barbiturate anesthesia even if the effects of this drug had certainly worn off. This is presumably due to the direct effect of the low temperature.

Of the 3 cats in which the caval veins were occluded for 30 minutes, 2 showed return to normal activity at the end of the experiment (see Fig. 5), in the third no activity was present. This third animal was, however, cooled at 18° C. and this may account for the difference.

In both the other animals a certain amount of activity was present during caval occlusion in the cortical and subcortical leads (Fig. 5, *C*). This indicates that the azygos flow is sufficient for a relatively normal functioning of the brain tissue at this low temperature.

4. *Brain activity in cats surviving the circulatory arrest for 20 minutes.* Four cats in which the venous inflow to the heart was interrupted for 20 minutes (venae cavae and azygos vein occluded) under hypothermia were kept alive at the end of the acute experiment.

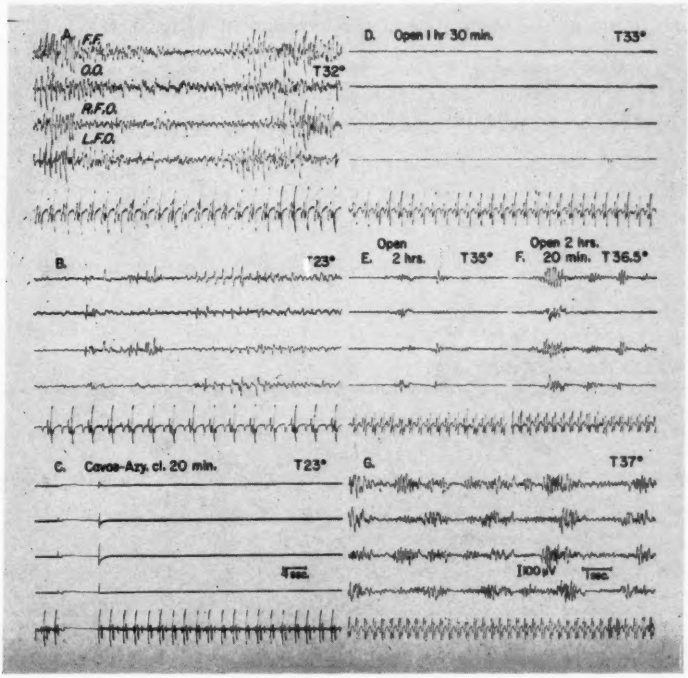


Fig. 6.—In this case, the cortical records remained silent for the longest time after reopening of circulation (20 minutes occlusion of caval and azygos veins).

A, At temperature 32° C. *B*, At temperature 23° C. *C*, Immediately before reopening of veins; time line in these records is 4 seconds. *D*, No activity present 1½ hours following *C*. The very first small bursts of spontaneous activity appeared 2 hours after reopening. *E*; and increase in amplitude in *F*, 2 hours 20 minutes after *C*; more numerous in *G* at 37° C.

All 4 started to breathe spontaneously about 1 hour before the chest and the scalp incisions were sutured. Parenteral fluids and penicillin were administered daily. Three cats made a complete recovery and electroencephalograms were taken in each at 36 hours, 3 days, and 5 days after the acute experiment. One of these experiments is illustrated in Figs. 6 and 7.

The initial records from four cortical leads is typical of barbiturate anesthesia. At 23° C., the barbiturate spindles are still recognizable even if diminished in amplitude and frequency (from 14 to 16 seconds to 7 to 8 seconds). A flat record, as expected, followed the closure of the three veins

(Fig. 6, *C*) and persisted for about 1 hour and 30 minutes following the opening of the clamps (Fig. 6, *D*). The total circulatory arrest was 20 minutes at 23° C. and no ventricular fibrillation occurred. The very first signs of cortical activity reappeared 2 hours after the clamps were released and consisted of short (3 to 4 seconds) bursts of low voltage oscillations separated by intervals of about 4 to 8 seconds during which the record was almost isoelectric. The rectal temperature was 36.5° C. at this time (Fig. 6, *E*). During the course of another hour the isoelectric intervals became progressively shorter and the amplitude of the individual bursts increased considerably. Only when the temperature reached 37° C., did the cortical activity begin to be comparable to the one found at the beginning of the experiment (Fig. 6, *G*).

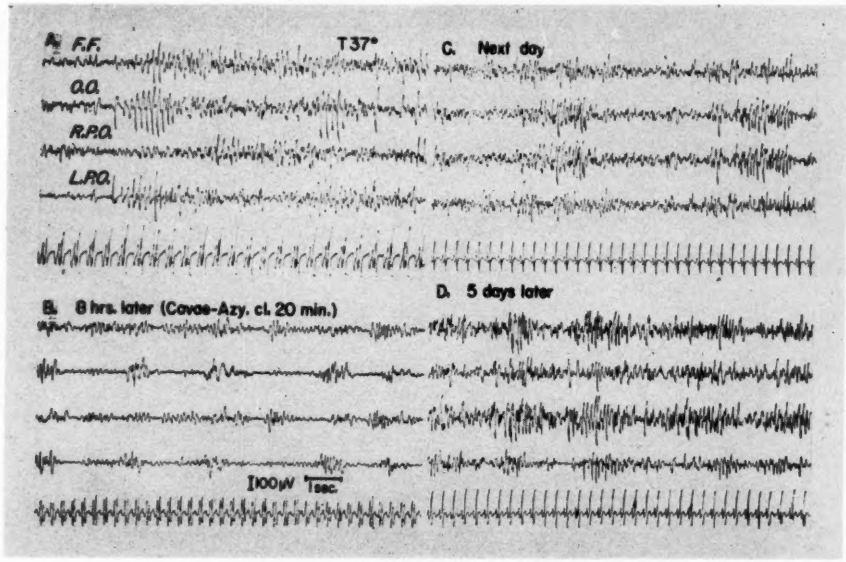


Fig. 7.—Same experiment illustrated in Fig. 6. *A*, At the beginning of the experiment. *B*, Eight hours later. *C*, EEG recorded the following day. *D*, Five days later.

It is worth noting that spindles similar to the ones induced by barbiturates are characteristic to these tracings 8 hours after beginning the procedure, when the effects of Nembutal were presumably absent. This is then a good example that during rewarming, following circulatory arrest, the cortical activity is not identical with that obtained during cooling when identical temperatures are compared. Records were taken from the same animal 1 and 5 days after the acute experiment (Fig. 7). These records are shown together with the tracings taken at the beginning and the end of the acute procedure (Fig. 7, *A* and *B*). With the exception of record *B* (at the end of the experiment) the others were taken an hour after Nembutal was administered and all of them from the identical cortical areas. Records *A*, *C*, and *D* are obviously similar. A comparison between *B* and *C* or *D* clearly shows the extent of the return to normal pattern.

An objection can be raised that the obvious differences between such records as *B* and *C* of Fig. 7 are due to the effect of Nembutal. Actually an attempt was made in this and most of the other experiments to modify the activity present at the end of the acute procedure by injecting various amounts of Nembutal. But it was constantly found that the administration of the drug resulted only in minor changes in amplitude of the records. In most cases there was a reduction of the amplitude, in 2 cases a small increase. In no instance, however, were these changes of such a magnitude as to affect the tracings significantly. In particular, the activity present between the spindle bursts was unaffected.

DISCUSSION

Our experiments clearly indicate that either in normal or in hypothermic cats, the azygos flow protects the brain from the immediate effects of vena caval occlusion.

At normal temperature and closure of both venae cavae, the azygos being open, the EEG is reduced in amplitude but the general pattern is maintained for as long as 10 minutes.

In hypothermic cats, the two caval veins could be clamped for as long as 30 minutes and have the EEG return to normal levels. Such long periods of circulatory arrest were not tolerated when the azygos vein was also occluded. According to Andreasen and Watson, the azygos blood flow rises from 18 to 106 c.c. per minute when the caval veins are clamped. Such an increase would account for the persistence of the EEG activity during caval occlusion.

The over-all diminution of blood flow is then reflected in the decrease in amplitude of the brain waves.

The changes of the EEG in animals subjected to hypothermia have been described by several authors (Ten Cate,[16] Bigelow,[2, 3] Gänshirt[9, 10] and their co-workers). Our own findings confirm the previous observations and support the general conclusions that frequency and voltage decrease almost linearly with lowering of the body temperature from 32° to 20° C.

This is true for the cortex as well as for the subcortical structures explored in our study, including the hypothalamus.

Other results of our experiments cannot be compared with findings of previous authors. The combined effects of hypothermia and circulatory arrest on the electrical activity of the brain have been investigated only by Gänshirt and associates[9] but, in their experiments, the circulation had been interrupted for 3 to 5 minutes only (1952). In that and following papers Gänshirt[10] stressed the lengthening of the recovery time of the electrical activity at temperatures below 32° C. and following short periods of complete ischemia (2 to 3 minutes). Most of their experiments were carried out on isolated and perfused cat's head and the authors admit that their results cannot necessarily be transferred to the "intact" animal.

Our experiments showed constantly that the return of the electrical activity is greatly delayed when circulatory arrest is performed in hypothermic animals.

Such delay may be about 2 to 3 hours in cases in which the central nervous system was deprived of blood supply for 20 minutes at body temperatures of 24 to 21° C.

It is difficult to explain the long electrical silence in both cortex and subcortex which follows the restarting of the circulation. This silence is certainly due to a temporary suspension of cellular activity which does not interfere with the return to normal function. This was demonstrated in those animals in which auditory potentials were recorded at the end of the acute experiments. The presence of such a response to a normal stimulus obviously indicates the integrity of the many nervous structures involved. This is the more surprising, considering that the general pattern of the EEG in these animals was far from being "normal" (Fig. 4). The temporary nature of the electrical silence following restarting of the circulation was further demonstrated by the return to normal activity 1 and 3 days after acute experiments were performed (Figs. 6 and 7).

As pointed out in the previous pages, the EEG at the end of the acute procedures was never "identical" with that taken at the beginning. Even in those cases in which the return to the initial pattern was almost complete, a reduction of amplitude was present.

Thus, there is good evidence that complete restitution of the EEG to pre-experimental levels cannot be expected within a short time in animals subjected to hypothermia combined with circulatory arrest. Whatever changes were present, at the end of the acute procedures, they disappeared when the animals were allowed to recover and records were taken 36 hours or 4 days later. In these experiments, as shown in Fig. 7, the EEG returned to a state practically identical with the pre-experimental status. An attempt to interpret this phenomenon, as well as the long electrical silence following the circulatory arrest, leads to some speculations.

The changes induced by hypothermia have been analyzed by Swan,[15] Bigelow[2, 3] (1952), Churchill-Davidson,[6] McMillan[14] and their colleagues. Such changes involve electrolyte balance, acid-base balance, oxygen dissociation, blood volume, and blood coagulation. There seems to be no agreement with regard to the changes in electrolyte balance. According to Swan (1953), serum sodium remains constant, and serum chloride rises slightly during hypothermia; in the opinion of Churchill-Davidson there is a fall in sodium and chloride. The fall in serum potassium and phosphorus, reported by Swan, in hyperventilated hypothermic dogs was not confirmed by Fleming[8] and McMillan[14] who reported instead a rise in serum calcium and of Ca/K ratio independent of type of respiration.

The changes in electrolyte balance whatever they might be, do not seem to be great enough to affect the brain activity at normal body temperature. Rubin and his associates (1943) did not find changes in the EEG of cats following intravenous injections of potassium chloride and calcium chloride (15 c.c. per minute) unless cardiac arrest developed; intravenous injection of sodium chloride (30 c.c.) was also without effect on the EEG.[11] It cannot be overlooked,

however, that they became effective during hypothermia. In this respect the findings of Elliott and Crimson (1947) (quoted by Swan[15]) indicate that doubling the blood potassium, ineffective in normothermic rats, produced cardiac arrest at 25° C.

Changes in pH have well-known effects on the EEG in normothermic animals, and the slowing of brain rhythms connected with overbreathing have common clinical applications.

In hypothermic animals, the pH changes depend on the type of respiration as was emphasized by Swan and his co-workers. From the data of Swan, it is clear that carbon dioxide content of the blood does not increase during the circulatory arrest. The carbon dioxide eliminated during circulatory arrest must then stay in the vicinity of the cells, lowering the tissue pH. A return to normal pH level would occur very rapidly at the restarting of the circulation. The effects of carbon dioxide accumulation have been extensively investigated with respect to the irritability of the myocardium and the origin of ventricular fibrillation and there is indication that a prompt oxygenation prevents changes in heart excitability leading to ventricular fibrillation. In the case of the nervous tissue, however, it appears difficult to visualize how a pH change in the extracellular fluid established during the circulatory arrest, would be directly responsible for the long lasting electrical silence which follows the restarting of the blood flow.

It appears legitimate to assume that the reopening of the blood flow associated with hyperventilation promptly restores the normal pH values. It is then probable that, besides the pH changes, some other mechanism is responsible for the long suspension of the spontaneous nervous activity.

Recent observations in clinical cases and in experimental animals indicate that the glucose metabolism is greatly altered during hypothermia (Wynn[17]). Since glucose metabolism is of primary importance for the nervous tissue it is likely that hypothermia and circulatory arrest, directly or through the pH changes, due to carbon dioxide accumulation, alter glucose metabolism so that the return to normal activity is greatly delayed.

In this respect it must be pointed out that in normothermic animals an increase in carbon dioxide is followed by an increase of lactate (Hill and Parr,[11] 1950). But since the steps of glucose metabolism are so numerous and involve a great number of enzymatic reactions, it appears futile to attempt a more detailed explanation of the electrical silence on this basis. Because of its duration, however, such silence is better understood on the assumption that a block of glucose metabolism occurs, probably connected with the obvious pH changes.

SUMMARY

The effects of hypothermia and circulatory arrest on the electrical activity of the cortex and subcortical structures have been studied in 18 cats lightly anesthetized with intravenous d-tubocurarine. In 6 out of 18 animals, the EEG returned to normal after complete circulatory arrest for 20 minutes at 25° to 23° C.

Longer periods of circulatory arrest (up to 30 minutes) were found compatible with a recovery of the EEG to normal when the azygos vein was not occluded. Hypothermia when combined with circulatory arrest is followed by long lasting electrical silence. The complete return to pre-experimental pattern was seen in animals sacrificed 3 and 5 days after the acute procedure.

The possible mechanism of the delayed return of the EEG to pre-experimental levels is discussed in the light of the systemic changes produced by hypothermia and circulatory arrest.

REFERENCES

1. Andreasen, A. T., and Watson, F.: Experimental Cardiovascular Surgery. Further Experiments on the Azygos Factor, Brit. J. Surg. **40**: 616-621, 1952.
2. Bigelow, W. G., Callaghan, J. C., and Hopps, J. A.: General Hypothermia for Experimental Intracardiac Surgery, Ann. Surg. **132**: 531-537, 1950.
3. Bigelow, W. G., Mustard, W. T., and Evans, J. G.: Some Physiological Concepts of Hypothermia and Their Application to Cardiac Surgery, J. THORACIC SURG. **28**: 463-480, 1954.
4. Callaghan, J. G., McQueen, D. A., and Scott, J. W.: Cerebral Effects of Experimental Hypothermia, A. M. A. Arch. Surg. **68**: 208-215, 1954.
5. Chatfield, P. D., Lyman, C. P., and Purpura, D. P.: Effects of Temperature on Spontaneous and Induced Electrical Activity in Cerebral Cortex of Golden Hamsters, Electroencephalog. & Clin. Neurophysiol. **3**: 225-230, 1951.
6. Churchill–Davidson, H. C.: Hypothermia, Brit. J. Anaesth. **27**: 313-318, 1955.
7. Cohen, M., and Lillehei, C. W.: A Quantitative Study of the "Azygos Factor" During Vena Caval Occlusion in Dog, Surg. Gynec. & Obst. **98**: 225-235, 1954.
8. Fleming, R.: Acid-base Balance of the Blood in Dogs at Reduced Body Temperature, A. M. A. Arch. Surg. **68**: 145-150, 1954.
9. Gänshirt, H., Dransfeld, L., and Zylka, W.: Das Hirnpotentialbild und der Erholungsrückstand am Warmblülergenhirn nach kompletter Ischämiae, Arch. Psychiat. **189**: 109-125, 1952.
10. Gänshirt, H., Krenkel, W., and Zylka, W.: The Electrocorticogram of the Brain at Temperatures Between 40° and 20° C. Electroencephalog. & Clin. Neurophysiol. **6**: 409-413, 1954.
11. Hill, D., and Parr, G.: Electroencephalography, London, 1950, McDonald & Co., pp. 127-160
12. Lam, R. C., Geoghegan, T., and Lepore, A.: Induced Cardiac Arrest for Intracardiac Surgical Procedures, J. THORACIC SURG. **30**: 620-626, 1955.
13. Lam, R. C., Geoghegan, T., Lepore, A., and Sergeant, C. K.: Induced Cardiac Arrest for Intracardiac Surgical Procedures. An Experimental Study, Proceedings of 29th Scientific Sessions of the Am. Heart Assoc., Oct. 26-29, 1956.
14. McMillan, I. K. R., Melrose, D. G., Churchill-Davidson, H. C., and Lynn, R. B.: Hypothermia: Some Observations on Blood Gas and Electrolyte Changes During Surface Cooling, Ann. Roy. Coll. Surgeons **16**: 186-194, 1955.
15. Swan, H., Zeavin, I., Holmes, I. H., and Montgomery, V.: Cessation of Circulation in General Hypothermia. I. Physiologic Changes and Their Control, Ann. Surg. **138**: 360-375, 1953.
16. Ten Cate, J., Horsten, G. P. M., and Koopman, L. J.: Influence of Body Temperature on E. E. G. of Rat, Electroencephalog. & Clin. Neurophysiol. **1**: 231-235, 1949.
17. Wynn, V.: Electrolyte Disturbances Associated With Failure to Metabolize Glucose During Hypothermia, Lancet **2**: 575-578, 1954.

TRANSVENTRICULAR MITRAL COMMISSUROTOMY

Surgical Technique and a Hemodynamic Evaluation of the Method

Andrew G. Morrow, M.D., and Nina S. Braunwald, M.D.,
Bethesda, Md.

IN THE FIRST operation carried out for the relief of rheumatic mitral stenosis, a transventricular approach to the valve was employed; in this operation, reported by Cutler and Levine[1] in 1923, the valve was incised by a knife passed through the wall of the left ventricle. Although the first patient operated upon by this method survived, the technique was subsequently abandoned in favor of the transatrial route devised by Souttar[2] in 1925 and his technique was adopted by all surgeons when operations for mitral stenosis were resumed in the 1940's. As experience with the operation accumulated it became apparent that an adequate commissurotomy could not be accomplished in many patients by digital fracture alone. Commissurotomy knives of various types were then developed and when these were employed by experienced surgeons many otherwise intractable valves could be satisfactorily opened. Digital fracture, combined when necessary with the use of a valvulotome, was employed at the National Heart Institute until 1958. The hemodynamic results of these operations, as determined by operative pressure records and postoperative left heart catheterizations, were considered inadequate in many patients. Thus, when transventricular mitral commissurotomy was described to the authors by Messrs. Andrew Logan and Oswald Tubbs as a more effective procedure, the method was adopted. Initial experiences with transventricular dilatation indicated that the anatomic result, as determined by palpation, was more uniformly adequate than after the conventional operation. A study was then undertaken to determine if these observations were supported by hemodynamic measurements. The diastolic pressure gradient across the mitral valve was measured before and after operation in 25 patients undergoing transventricular commissurotomy and these data were compared to similar measurements which had been obtained previously in patients operated upon by the transatrial route. The results of this hemodynamic study and a description of the technique of transventricular mitral commissurotomy are presented in the present report.

MATERIAL

Operative records of left atrial and left ventricular pressures were available in 50 patients operated upon for mitral stenosis immediately prior to the adoption

From the Clinic of Surgery, National Heart Institute, Bethesda, Md.
Received for publication Jan. 15, 1960.

of the transventricular operation. These patients constitute the control series. In these patients, the valve had been approached through the left atrium and a digital commissurotomy was attempted in every instance. If a satisfactory finger-fracture could not be achieved, the commissures were cut with one of several varieties of valvulotomes. Such instruments were employed in approximately 25 per cent of the operations. Left atrial and left ventricular pressures were also measured simultaneously in 25 patients before and after the valve was

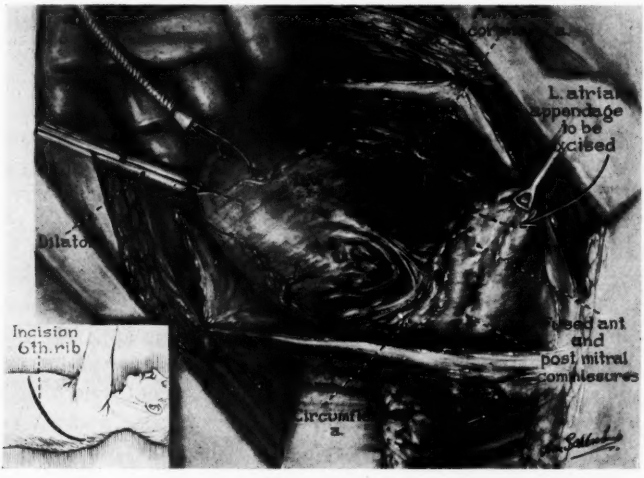


Fig. 1.—Operative preparations for transventricular mitral commissurotomy. Both the mattress suture in the apex of the left ventricle and the purse-string suture about the atrial appendage are placed before the valve is explored.

opened by transventricular dilatation. In every patient the diastolic gradient across the valve was measured after the first 0.1 second of diastole and at the end of diastole. In addition, the mean atrioventricular diastolic gradient was determined by planimetric integration of the pressure difference throughout diastole. The pressures were measured with 20 gauge needles attached to Statham P 23 D pressure transducers and recorded on a direct-writing or photographic oscillograph.

The two series of patients are comparable in regard to the degree of compensation and symptomatology. The sex distribution was similar and the mean age of control patients was 35 years as compared to a mean age of 37 years in the patients who underwent transventricular operation.

TECHNIQUE

The patient is placed in lateral position and a standard posterolateral thoracotomy is made with resection of the sixth rib. This incision, carried far anteriorly, affords good exposure of the left atrial appendage as well as the apex of the ventricle. The pericardium is incised anteriorly from the apex of the heart to the reflection on the left pulmonary artery and it is suspended by traction sutures (Fig. 1). After pressures in the left atrium and left ventricle

have been recorded, the left atrial appendage is circumscribed with a purse-string suture. The heart is then delivered from the pericardium and a mattress suture of No. 5 silk is placed in an avascular area at the apex of the left ventricle. This suture is attached to a Rumel tourniquet. The atrial appendage is then incised and the index finger inserted. A careful assessment is made of the size and position of the valve orifice, the presence and severity of any regurgitation, the mobility of each leaflet, and the presence and distribution of calcification, if this is present. An attempt is then made to open the valve by digital separation of the fused commissures. If the anterior commissure can be separated easily

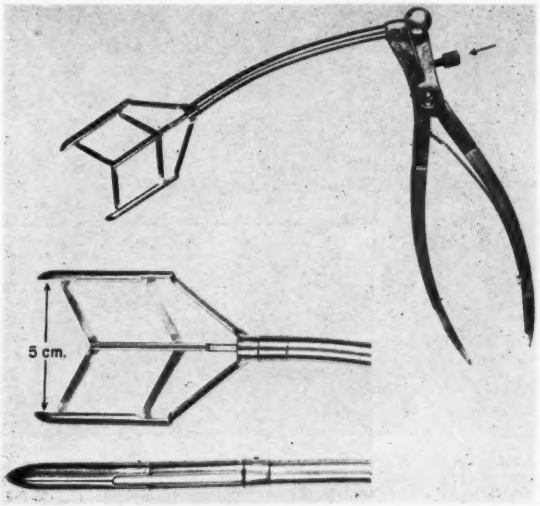


Fig. 2.—The two-bladed dilator devised by Mr. O. S. Tubbs which is used in transventricular mitral commissurotomy. The extent to which the blades open is regulated by the screw indicated by the arrow.

and completely to the annulus, transventricular dilatation is considered unnecessary. Such favorable valves are encountered in less than 15 per cent of patients at this clinic and more usually a rubbery, fibrotic, or calcific orifice precludes an adequate digital commissurotomy. Under these circumstances the procedure is completed by the transventricular route. A small epicardial incision is made within the mattress suture while the right index finger remains within the atrium. The two-bladed dilator* (Fig. 2) is then introduced into the ventricle and bleeding around it is controlled with the Rumel tourniquet. The tip of the dilator is guided through the valve orifice with the aid of the palpating finger in the atrium. The blades of the instrument are then positioned in the line of the commissures and, in most instances, opened to their fullest extent, 5 cm. (Fig. 3). In patients with small hearts, the extent of dilatation may be limited to 3.5 or 4.0 cm. by adjustment of the regulating screw on the instrument prior to its introduction. The dilator is then closed and retracted into the ventricle and the

*Manufactured by the Genitourinary Manufacturing Co., Ltd., London, England.

results of the procedure assessed. Further instrumentation can be carried out if it is deemed necessary. The dilator and finger are then withdrawn as the mattress and purse-string sutures are tied. The atrial appendage is oversewn with a continuous suture and the ventricular incision is reinforced with several fine interrupted sutures. After measurements of left atrial and left ventricular pressures have been repeated, the pericardium is loosely approximated, a drainage tube is inserted, and the chest is closed.

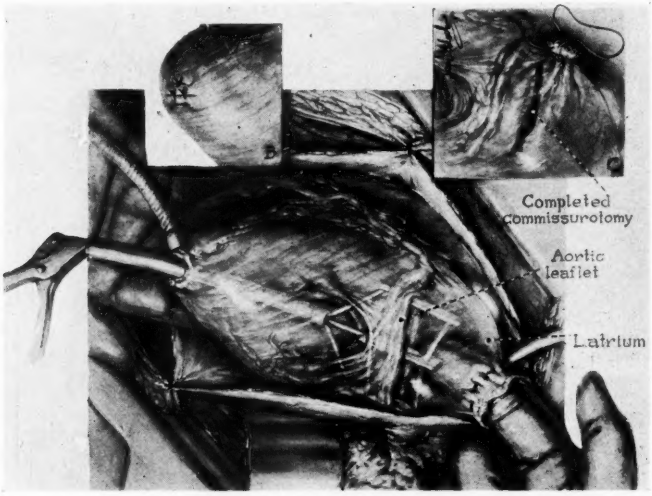


Fig. 3.—Transventricular fracture of the mitral valve. The dilator is positioned and the results of dilatation are assessed by the palpating finger within the atrium. After commissurotomy the ventricle *(B)* and atrium *(C)* are closed as shown.

RESULTS

The adequacy of operative treatment was evaluated in all patients by comparing the operative records of left atrial and left ventricular pressures obtained before and after commissurotomy. Typical tracings obtained in a patient with a favorable valve are reproduced in Fig. 4. The 0.1 second, the end-diastolic and mean atrioventricular gradients for all patients are listed in Table I. The heart rate and blood pressure (not tabulated) were similar at the times of pre- and postoperative measurements. The mean diastolic gradients before and after commissurotomy are shown graphically in Fig. 5. It is apparent from inspection of the plotted gradients obtained in control patients, in whom the valve was opened by finger fracture or a knife, that, in a large proportion of them, significant obstruction was still present after commissurotomy. Analysis of these data reveals that in the control patients the average mean diastolic gradient before operation was 13.3 mm. Hg and after commissurotomy 8.4 mm. Hg. Thus, the gradient was reduced by only 29 per cent in this group. In the patients operated upon by the transventricular route these average gradients before and after operation were 16.1 and 6.1 mm. Hg, respectively. This procedure resulted in an average reduction of the gradient of 62 per cent. It can also

be seen from the graph that following the transventricular operation only 5 of 25 patients had residual gradients greater than 8 mm. Hg and 4 of these patients were among the 5 with the most severe obstruction before operation. In contrast,

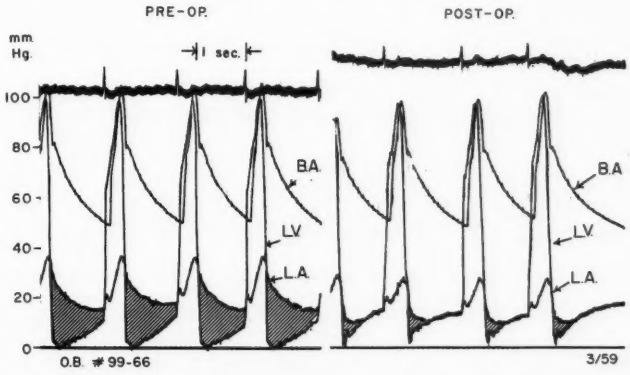


Fig. 4.—Operative records of left atrial *(L. A.)*, left ventricular *(L. V.)* and brachial arterial *(B. A.)* pressures before and after transventricular mitral commissurotomy (Patient O. B.). The hatched areas indicate the mean diastolic pressure gradient. No end-diastolic gradient is present after commissurotomy and the mean gradient is reduced from 18 to 4 mm. Hg.

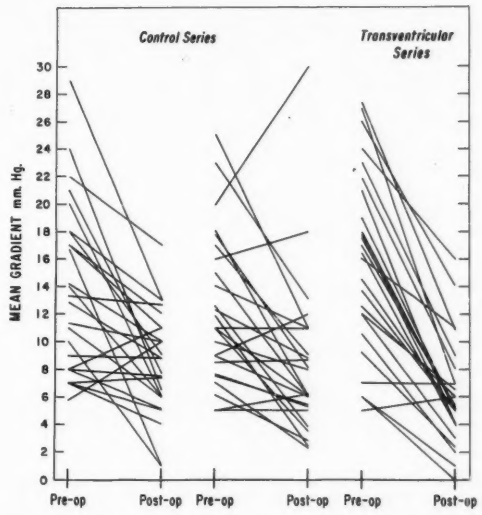


Fig. 5.—Mean diastolic mitral valve gradients before and after mitral commissurotomy performed by the conventional method (control series) or by transventricular dilatation. An analysis of these data is presented in the text.

the residual gradient was greater than 8 mm. Hg in 24 of the 50 patients in whom the valve was opened by conventional means. Although only the mean diastolic gradients are plotted in Fig. 5, the changes were usually similar in the pressures measured at 0.1 second and at the end of diastole.

TABLE I. OPERATIVE RECORDS OF THE MITRAL VALVE GRADIENTS AND HEART RATES BEFORE AND AFTER CONVENTIONAL AND TRANSVENTRICULAR MITRAL COMMISSUROTOMY*

CONTROL SERIES											TRANSVENTRICULAR SERIES				
		GRADIENT			HEART		GRADIENT			HEART		GRADIENT			HEART
PATIENT	STATUS	0.1	END	MEAN	RATE	PATIENT	0.1	END	MEAN	RATE	PATIENT	0.1	END	MEAN	RATE
R. B.	Preop.	13	5	11.4	70	A. A.	16	10	17	60	P. A.	14	20	21	60
01-73-29	Postop.	12	3	10	70	00-95-97	13	4	9	60	02-55-97	8	4	4	75
J. B.	Preop.	10	16	14.2	75	P. A.	10	15	14	80	P. A.	6-8	6-7	5	80
01-64-31	Postop.	3	9	10	66	00-78-06	12	10	11	90	00-78-06	5-6	5-6	6	90
A. B.	Preop.	13	5	9	60	T. B.	8	2	6.1	70	O. B.	20-24	6	17.8	42
01-71-71	Postop.	12	5	8.8	60	01-94-58	2.3	0	2.8	60	00-99-65	2-5	0	4	42
E. C.	Preop.	8	8	8	90	M. B.	16	14	16	75	I. C.	11	5	7	90
01-63-56	Postop.	9	9	11	95	00-92-66	20	20	18	90	02-36-59	11	5	6.9	90
B. C.	Preop.	12	21	20	90	L. B.	14	5	11	48	D. C.	20	17	22	
01-42-05	Postop.	6	6	6	90	00-78-49	8	2	6	52	02-32-87	11	8	8	
H. C.	Preop.	13	2-3	7	130	D. G.	10	8	8.5	60	C. C.	20	18	17	75
01-70-33	Postop.	8	2	7.4	130	00-98-41	11	6	8.7	69	02-31-96	10	5	5.3	75
M. D.	Preop.	13	10	8	60	A. G.	11	13	12.5	70	J. C.	24	28	27.5	70
01-34-52	Postop.	13	10	7.5	65	01-82-38	4.5	5	3.7	70	02-35-85	9	9	10.8	90
H. D.	Preop.	11	10	13.3	65	M. G.	22	16	18	85	M. E.	14	5	14.5	70
01-66-38	Postop.	12	3	12.6	70	00-95-99	9	4	6	95	02-39-39	8	4	5	80
M. D.	Preop.	24	5	16.7	110	B. G.	14	5	11.9	68	S. G.	15-20	7	12	
01-82-40	Postop.	2	0	1	110	01-97-14	3.4	0	2.4	78	02-12-42	8	6	6.5	
E. D.	Preop.	8	0	7	48	H. H.	10	5	9	45	H. H.	8	6	6	85
01-46-81	Postop.	6	2	4	55	00-83-99	8	4	6	45	02-57-02	1-2	1	1	90
F. E.	Preop.	22	15	18	95	A. I.	9	3	7	110	V. J.	22	15	18	63
01-45-49	Postop.	14	10	13	75	00-77-27	4	2	2-3	100	00-86-72	5	3	5	86
M. F.	Preop.	27	18	21	70	D. K.	8.9	2	5	65	E. J.	16-20	16	16.5	74
01-59-61	Postop.	13	4	7.7	70	00-77-25	10-11	4	6.2	90	02-25-06	2-4	4-5	4	60

J. G.	Preop.	12	21	17	55	W. L.	28	16	17.8	65	F. J.	26	19	23	80
01-58-91	Postop.	18	12	12	60	01-89-67	15	2	8.2	90	02-44-49	9	3	9	70
D. G.	Preop.	28	26	24	80	W. L.	25	20	23	78	C. K.	28	20	24	75
01-68-84	Postop.	6	1.2	6.3	50	02-04-23	14	10	13	78	00-24-01	18-20	10	16	75
R. H.	Preop.	12	10	10	46	J. McG.	11	5	7.6	75	P. K.	7	10	6	67
01-86-90	Postop.	1	0	0-1	65	01-89-68	10	3	5.3	80	02-46-19	1	0	0	65
W. M.	Preop.	22	10	17	80	A. M.	8	2	5	75	R. P.	28	20	26	62
01-53-19	Postop.	12	10	11	55	02-06-40	8	2	5	75	02-18-52	17	10	14	70
J. M.	Preop.	22	7	14	55	R. M.	18	8	9	55	R. P.	16	10	9.2	60
01-44-40	Postop.	13	0	6	60	00-79-14	20	2	12	70	02-27-25	10	2	2.3	62
D. McK.	Preop.	13	5	8	80	D. O.	16	10	12.3	50	W. P.	24	15	27	50
01-71-21	Postop.	6.7	4	5.1	78	02-00-59	14	5	8.8	50	02-41-94	10-12	5	6.8	85
T. O.	Preop.	14	0	7	65	A. R.	16	5	11	70	M. P.	16	6-8	13.7	45
01-42-91	Postop.	10	0	5	70	00-94-09	6	2	3.5	78	02-19-74	4-5	2	5	65
M. P.	Preop.	14	15	12.8	72	C. R.	21	10	15	70	L. R.	20	10-12	17.6	75
01-68-28	Postop.	10	8	8.8	70	01-98-23	10	5	6	70	02-24-61	10	5	5.3	72
J. R.	Preop.	22	15	22	100	K. S.	30	15	25	82	A. R.	16	5-6	12-13	60
01-43-47	Postop.	19	7	17	75	01-83-44	15	3-4	11	70	02-21-73	10	4	6	60
W. S.	Preop.	10	14	11	90	M. S.	20	10	20	140	C. S.	15	16	16	55
01-87-35	Postop.	4	2	6	90	00-86-70	30	11	30	130	02-40-04	10	6	11	60
H. S.	Preop.	27	22	29	100	G. V.	14	5	10	60	E. T.	12	18	10.6	90
01-51-34	Postop.	13	9	13	85	00-86-69	10	3-4	8	76	00-86-08	2-3	0	2	85
D. S.	Preop.	7.5	0-1	5.8	48	E. W.	15	4	7.5	59	J. T.	20	4	19	62
01-70-02	Postop.	11	2	10	50	00-88-45	14	0	5.4	70	02-46-16	8	1	5.2	80
L. T.	Preop.	20	11	18	60	J. W.	24	8	11	44	E. T.	15-18	5	12	80
01-49-54	Postop.	11	3	9	45	01-91-68	21	8	11	60	02-17-48	8	5	3	70

*All gradients are expressed as mm. Hg and are defined in the text.

It should be noted that in some instances the diastolic gradient across the mitral valve was found to be higher after commissurotomy than before. Since the magnitude of the pressure gradient across the mitral valve is dependent upon the rate of blood flow through the stenotic orifice as well as the size of the orifice, gross increases in valve flow after commissurotomy can result in higher gradients. Whenever gross mitral regurgitation is produced, valve flow is increased and this was the usual cause of higher postoperative gradients in the control patients. No significant mitral regurgitation occurred in any patient after transventricular commissurotomy. One patient in this group died of renal failure 8 days after operation, an operative mortality rate similar to that in the control series.

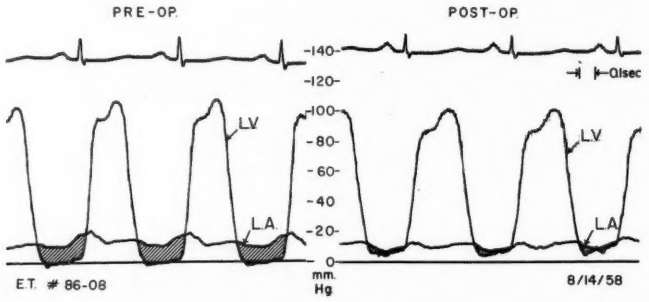


Fig. 6.—Operative records of left atrial and left ventricular pressures before and after transventricular mitral commissurotomy in a patient (E. T.) who had had a previous operation without relief of obstruction. The end-diastolic gradient is abolished and the mean gradient reduced from 12 to 2.5 mm. Hg.

Three of the patients in whom the transventricular approach was employed had had previous digital mitral commissurotomies with residual stenosis of severe degree. In each, an anatomically unfavorable valve was present, but in 2 of the 3 patients a satisfactory hemodynamic result was achieved when the valve was opened with the dilator (Fig. 6). In 3 other patients, with combined aortic stenosis and mitral stenosis, both mitral and aortic commissurotomies were carried out by the transventricular route. The somewhat smaller and longer instrument described by Glover was used for the aortic valve. In each of these patients, an adequate fall in the mitral gradient was noted. In 1 patient tricuspid stenosis accompanied mitral stenosis and both valves were opened with the dilator. After mitral commissurotomy, the instrument was inserted through an incision in the right ventricle and the tricuspid valve easily opened. In this patient both valves were of fibrous and rubbery consistency and had resisted digital fracture.

DISCUSSION

The difficulties inherent in evaluating the results of operations for mitral stenosis are widely appreciated.[3, 4] Neither clinical appraisal of the patients after operation nor the surgeon's description of the valve after commissurotomy provides a standard sufficiently objective for critical analysis. A comparison of

the pressure gradient across the valve before and after the procedure is a far more reliable index of the operative result.[5, 6, 7] Complete abolition of the pressure gradient is indicative of complete relief of obstruction to blood flow and the surgical method which most nearly accomplishes this end will most often provide benefit. As noted previously,[5] a determination of cardiac output at the time by pressure gradient is measured is desirable. When both the rate of blood flow through the valve and the pressure gradient across it are known, the actual area of the stenotic orifice may be calculated from hydraulic formulae. Unfortunately such combined studies were not carried out in a sufficient number of these patients to permit a comparison of the results of the two operations on this basis.

In the group of patients in whom the valve was opened by digital fracture or the use of a knife, postoperative measurements of the valve gradient indicated that it had been reduced to less than 8 mm. Hg in only 52 per cent. In contrast, when the transventricular operation was employed, a satisfactory relief of the stenosis was achieved in 80 per cent of the patients. A mean gradient of 8 mm. Hg is used as a somewhat arbitrary standard, since gradients of this magnitude or less ordinarily reflect a mean left atrial pressure which is only slightly elevated and seldom responsible for symptoms or disability. The advantage of the transventricular operation is further magnified by the fact that the valves most suitable for treatment, that is, those which opened easily and completely with digital pressure, were not included in the transventricular series. This difference in selection is also reflected in the preoperative gradients measured in the two groups. The average mean diastolic gradient in the control patients was 13.3 mm. Hg while the increased severity of stenosis in the patients in whom the transventricular operation was employed is indicated by an average gradient of 16.1 mm. Hg. In both groups there were a large number of severely deformed valves, perhaps reflecting the group of patients with advanced disease who are often referred to this clinic; more than half of all patients were over 40 years of age.

In most instances there was good correlation between the change in the mean pressure gradient and that in the 0.1 second and end-diastolic gradients (see Table I). However, in an occasional patient, the alteration in one of the gradients was at variance with the other two. Since the 0.1 second and end-diastolic gradients represent only single points during diastole and the mean diastolic gradient measures the average change throughout this portion of the cycle, the latter value was considered more meaningful in characterizing the hemodynamic result.

When the transventricular dilator was first employed it was felt that the blades of the instrument should be carefully positioned in the axis of the commissures. Experience soon proved, however, that the position is not critical and the swivel head of the dilator adapts itself to the commissures as they open. In all instances the valve appears to open first at the point of least dense fusion—ordinarily the anterior commissure but sometimes the posterior. Further dilatation will ordinarily effect complete separation in both regions if this is deemed

desirable. If, on the other hand, regurgitation through the posterior commissure is already present the opening can be confined anteriorly. Experiences with the correction, under direct vision, of congenital mitral stenosis indicate that, in this lesion, true commissures are not present, and the relation of the valve orifice to the papillary muscles supporting it is such that dilatation would likely result in a torn leaflet.

Among patients who had no palpable evidence of mitral regurgitation before commissurotomy, this lesion was never produced by transventricular dilation. When minimal regurgitation was present, usually at the posterior commissure, it was never aggravated by the procedure. These results are in contrast to the experience in this clinic when a commissurotomy knife was employed. Unless the cut, which is made blindly, could be precisely localized to the commissure, severe regurgitation was often a sequel.

The transventricular operation for mitral stenosis which has been described was devised in 1954 by Mr. Andrew Logan of Edinburgh. He, at first, employed a dilator passed from the atrium, the method described by Dubost,[8] but soon found that the procedure was easier and safer when the instrument was introduced from the ventricle.[9] Although the transventricular operation is almost universally employed in the United Kingdom, experience with the procedure in this country is, as yet, not extensive.[10, 11] As the advantages of the method become better known, however, it will undoubtedly be more widely utilized.

SUMMARY

The hemodynamic results of mitral commissurotomy were determined in 50 patients in whom the valve was opened by digital fracture or a valvulotome and in 25 patients in whom transventricular commissurotomy was performed. With the transventricular operation the mean diastolic pressure gradient across the valve was decreased by an average of 62 per cent. In patients in whom the conventional operation was employed the reduction averaged only 29 per cent. Mitral regurgitation was never produced or aggravated by the dilator. The results of the study indicate that transventricular mitral commissurotomy is a safe and practical technique and effectively relieves mitral obstruction with minimal risk.

REFERENCES

1. Cutler, E. C., and Levine, S. A.: Cardiotomy and Valvulotomy for Mitral Stenosis. Experimental Observations and Clinical Notes Concerning Operated Case With Recovery, Boston M. & S. J. **188**: 1023, 1923.
2. Souttar, H. S.: Surgical Treatment of Mitral Stenosis, Brit. M. J. **2**: 603, 1923.
3. Soloff, L. A., and Zatuchni, J.: Some Difficulties in Evaluating Functional Results After Mitral Commissurotomy, J. A. M. A. **154**: 673, 1954.
4. Bergy, G. C., and Bruce, R. A.: Discrepancies Between Subjective and Objective Responses to Mitral Commissurotomy, New England J. Med. **253**: 21, 1955.
5. Tanenbaum, H. L., Braunwald, E., and Morrow, A. G.: Determination of Cardiac Output and Pressure Gradients at Operation, New England J. Med. **258**: 527, 1958.
6. Moscovitz, H. L., Gordon, A. J., Braunwald, E., Amram, S. S., Sapin, S. O., Lasser, R. P., Himmelstein, A., and Ravitch, M. M.: The Use of Simultaneous Left Heart Pressure Pulse Measurements in Evaluating the Effects of Mitral Valve Surgery, Am. J. Med. **18**: 406, 1955.

7. Morrow, A. G., Braunwald, E., Haller, J. A., Jr., and Sharp, E. H.: Left Heart Catheterization by the Transbronchial Route. Technique and Applications in Physiologic and Diagnostic Investigations, Circulation **16**: 1033, 1957.
8. Dubost, M. C.: Presentation d'un nouvel instrument dilatateur pour commissurotomie mitrale, Presse med. **62**: 253, 1954.
9. Logan, A., and Turner, R.: Surgical Treatment of Mitral Stenosis, With Particular Reference to the Transventricular Approach With a Mechanical Dilator, Lancet **2**: 874, 1959.
10. Cooley, D. A., and Stoneburner, J. M.: Transventricular Mitral Commissurotomy, Surgery **46**: 414, 1959.
11. Gerbode, F.: Transventricular Mitral Valvotomy, Am. Heart J. (In press.)

TRANSVENTRICULAR MITRAL VALVULOTOMY UNDER CONTROLLED HYPOTENSION

V. O. Björk, M.D., M. H:son Holmdahl, M.D., and B. Löf, M.D., Uppsala, Sweden

THE finger fracture method for valvulotomy will not give an entirely satisfactory result in many cases. On one occasion, when too much force was used, the anterior left atrial wall was torn away from the ventricle. The reapproximation of the atrium to the ventricle was made by mattress sutures under the circumflex artery followed by recovery. (Other surgeons have encountered the same accident with a fatal outcome in several instances.) The great number of mitral knives available proves only that none is ideal. It was therefore a great step forward when Dubost[3] advocated the use of an expanding dilator, introduced through the left atrial appendage after a preliminary digital palpation and dilatation of the valve. The disadvantage of the method was the blind manipulation of the dilator inside the heart. Once during operation on a very densely fibrotic mitral ring, great force was applied to the dilator causing it to slip down into the small left ventricle rupturing its posterior wall. The patient died on the table. Several similar accidents are reported by Dubost.

None of the methods just mentioned is suitable for re-operation of mitral stenosis or in cases of thrombosed auricular appendage. After personal experience with these methods, it was easy to appreciate the superiority of the transventricular route advocated by Logan.[7] Even with open heart surgery with the use of a heart-lung machine, nothing more can be achieved than is possible with transventricular dilatation.[2]

MATERIAL

One hundred and fifty patients with mitral stenosis, operated upon by the same surgeon (V. O. B.), constitute the basis of this report. In 22 patients the aortic orifice was dilated at the same operation. In 9 of these 22 cases, a pressure gradient above the aortic ostium of more than 20 mm. Hg was found. The oldest patient in the series was 59 years of age and the youngest 20 years of age. The anesthesia and surgical techniques will be presented only for the last 75 operations for transventricular dilatation performed at the University Clinic of Uppsala.

From the University Hospital, Uppsala, Sweden.
Received for publication Feb. 3, 1960.

TECHNIQUE OF ANESTHESIA

All patients were premedicated with pethidine (25-75 mg.) and atropine (0.5 mg.), and 40 received Phenergan (25 to 50 mg.) in addition.

Before and during induction of anesthesia with a small dose of Pentothal (thiopentone) (minimum, 175 mg.; maximum, 350 mg.), all patients breathed oxygen. In patients with a previous history of pulmonary edema, intravenous barbiturate was completely omitted so as not to depress the myocardium; in these pure gaseous induction was used–oxygen, followed by nitrous oxide-oxygen.[4]

The anesthesia was maintained with nitrous oxide, with tubocurarine (mean total dose, 42 mg.—minimum, 20 mg.; maximum, 70 mg.) being used for relaxation. Ventilation was maintained by an Engström respirator, using a semi-open system with a minute volume of at least 8 L. (5 to 6 L. nitrous oxide, 3 to 2 L. oxygen).

In the first 10 cases the dilatation was performed without the aid of induced hypotension. In an attempt to reduce the bleeding and to facilitate the closure of the small incision in the left ventricle, we thereafter used Arfonad in all patients with a blood pressure above 90 mm. Hg immediately before dilatation in order to get a short period of hypotension during the dilatation.

Fifty-six patients received Arfonad. As a rule, a first dose of 5 to 20 mg. of Arfonad was injected intravenously, followed by additional 5 to 10 mg. doses every second minute until a blood pressure of 60 to 80 mm. Hg was reached. The magnitude of the first dose was determined by the stability rather than by the level of the blood pressure during the preceding period of the operation. The more stable the blood pressure, the larger the initial dose could be without an undesirable large fall in blood pressure. The mean total dose was 20 mg. (minimum, 5 mg.; maximum, 60 mg.).

In order to measure blood pressure exactly, a polyethylene catheter was inserted into the brachial or radial artery, using a modified Seldinger's technique of puncture.[6] In this way continuous recording of pressure could be made.

The mean blood pressure fall was 72 mm. Hg (minimum, 20; maximum, 175). The lowest blood pressure after Arfonad and dilatation averaged 60 mm. Hg. If the pressure did not begin to rise after dilatation and subsequent closure of the small ventriculotomy, Vasoxine (methoxamine) (mean, 10 mg.—minimum, 5 mg.; maximum, 20 mg.) was injected intravenously. The mean period of induced hypotension, that is, the period of a blood pressure below 90 mm. Hg, was 12 minutes (minimum, 8 min.; maximum, 20 min.). In 7 patients the systolic pressure fell below 40 mm. Hg, but in 6 of them it recovered rapidly after the use of Vasoxine. In only 1 of them was intermittent cardiac compression necessary and that patient made an uneventful recovery.

During the period of induced hypotension the percentage of oxygen in the respiratory mixture was increased to 50 per cent. Continuous electrocardiogram

monitoring was practiced in all cases. Besides ventricular extrasystoles during manipulation of the heart, there was little evidence of excessive myocardial irritability in spite of the very light anesthesia.

As a rule, the patients received atropine (0.5 mg.) and Prostigmin (0.5 to 2.5 mg.) before extubation for reversal of curarization.

SURGICAL TECHNIQUE

Digital commissurotomy was performed in 60 cases and in 9 of these a knife was also used. Transatrial dilatation, according to Dubost,[3] was used in 7 cases and transventricular dilatation, according to Logan,[7] in the remaining 83 cases.

Present Technique.—With the patient under general anesthesia, placed on his right side, an incision is made subcostally under the left fifth rib. The pericardium is opened anteriorly and parallel to the phrenic nerve. Then, in a place near the apex of the left ventricle free of large coronary vessels, a purse-string suture of 3-0 silk is inserted. No traction on this suture is used during the procedure, it is inserted only to facilitate hemostasis after removal of the dilator. An oblique incision is then made in the myocardium of the left ventricle in the center of the purse-string suture. The patient's blood pressure is now reduced to less than 80 mm. Hg by an intravenous injection of Arfonad before attention is directed toward the auricular appendage.

A suture is not placed around the left auricular appendage nor palpation made of the appendage in order to avoid dislodgment of thrombi. A hole, the size of the index finger, is made in the tip of the appendix and a generous flush of blood allowed to escape until it is evident that no thrombotic material remains in the appendix. The index finger is then introduced into the valvular area to evaluate possible regurgitation, the size of the orifice, and the valvular mobility. No attempt is made to open the valve by finger fracture. Then the dilator is pushed into the left ventricle through the incision at the apex and is guided to the mitral orifice. It is most important to introduce the instrument at the very apex of the heart to avoid it becoming entangled in the papillary muscles or chordae tendineae. The dilator must be introduced sufficiently far into the atrium so that the expanding blades do not protrude through the ventriculotomy incision. When the dilator is lying against the tip of the finger in the left atrium it is opened (Fig. 1). It has not been found necessary to open the dilator in the direction of the valvular orifice, exerting pressure on each commissure. The same result is obtained after expansion in any direction, although I have aimed at a dilation in the direction of the valvular orifice. If dislodgment of the auricular thrombi or of calcified fragments from the mitral valve is anticipated, the common carotid arteries in the neck may be compressed briefly by the anesthetist to reduce the danger of cerebral embolism. Occlusion of the innominate and left common carotid arteries after dissection of these vessels at their origin from the aortic arch, is not indicated. The valve is dilated widely from 3.5 up to 4.5 cm., depending on the size of the heart. Usually the dilator is opened to 4 cm. which corresponds

to 2 fingerbreadths. The instrument is opened several times in the mitral orifice, although usually nothing more is gained after the first dilatation. The dilator, however, often tends to slip into the atrium without opening the orifice and must therefore be kept firmly in place and the result checked before it is closed and removed from the ventricle while the purse-string suture is being tied. The incision in the ventricle is reinforced by two fine silk sutures after the index finger is withdrawn from the atrium. The pericardium is loosely closed. The wound is closed with two tubes for suction drainage. The same technique has been utilized for re-operation and, in my experience, there has been no need for a bilateral approach as used by Cooley.[2]

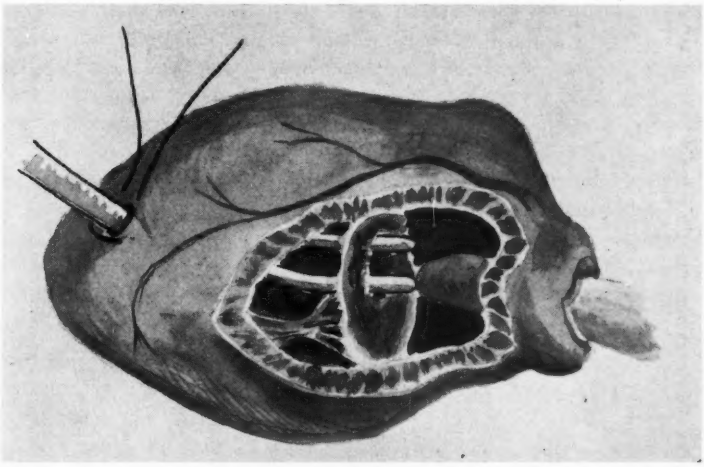


Fig. 1.—During the dilatation, one branch of the dilator is pressed the whole time against the finger tip for continuous control of its position. If the dilator is introduced at the apex of the left ventricle the lateral papillary muscle is avoided.

RESULTS

Mortality.—There was an over-all mortality rate of 9 per cent in the 150 cases. The rate was the same in the groups having transventricular dilatation or digital commissurotomy. A simultaneous dilatation of the aortic ostium carried a higher mortality, 18 per cent. The cause of death in the first 75 cases is shown in Table I.

TABLE I. THE CAUSE OF DEATH IN THE FIRST 75 CASES

DIAGNOSIS	SURGICAL TECHNIQUE	CAUSE OF DEATH
Mitral stenosis	Transatrial dilatation	Rupture of left ventricle
Mitral stenosis	Transventricular dilatation	Rupture of papillary muscle
Aortic stenosis + mitral stenosis	Transventricular dilatation	Brain embolism
Mitral stenosis	Digital commissurotomy	Brain embolism
Mitral stenosis	Digital commissurotomy	Heart failure
Mitral stenosis	Digital commissurotomy	Ventricular fibrillation due to active myocarditis

TABLE II. ANALYSIS OF CASES OF DEATH AFTER TRANSVENTRICULAR DILATATION OF THE MITRAL AND AORTIC OSTEA*

NO.	SEX	AGE (YEARS)	DIAGNOSIS	PRESSURES IN MM. Hg			AORTIC GRADIENT	HEART VOL. (ML./SQ. M.)	GROUP	TIME AND CAUSE OF DEATH
				PC	PA REST	PA WORK				
1	F	49	MS	38	104/46	—	—	900	IV	22 days after operation; pulmonary embolism
2	F	44	AS + MS + TS reoperation	25	46/21	—	100	1080	IV	On the table; rupture of an aortic cusp with insufficiency
3	F	46	AS + MS	28	107/51	—	40	820	IV	On the table; rupture of an aortic cusp with insufficiency
4	M	23	MS	24	56/25	108/56	—	795	II	4 days after operation; brain embolism
5	M	59	MS + carcinoma of the stomach	17	35/15	59/20	—	680	III	12 days after operation; emboli in brain, kidney and lung Commissurotomy and total gastrectomy with interposition of a jejunal loop between esophagus and duodenum, performed in one stage
6	M	42	MS	24	44/23	94/46	—	880	IV	One day after operation; emboli in left carotid, superior mesenteric, splenic, and right iliac arteries
7	F	45	MS + AS reoperation	30	70/—	—	20	690	IV	Six weeks after operation; heart failure, renal embolism

*There were 3 deaths in 19 cases in which Arfonad was not used (Cases 1, 2, 3) and 4 deaths in a series of 56 cases in which Arfonad was used (Cases 4, 5, 6, 7).

Abbreviations: AS = aortic stenosis; MS = mitral stenosis; TS = tricuspid stenosis; PC = mean pulmonary capillary pressure; PA = pulmonary artery pressure, systolic and diastolic; aortic gradient = systolic pressure gradient over the aortic valves. The cases are classified according to the American Heart Association.

In order to evaluate the influence of Arfonad on the mortality rate, the last 75 cases of transventricular dilatations anesthetized in Uppsala were analyzed (Table II). It is apparent that the hypotensive anesthesia was not responsible for any death.

Complications.—In 1 case, pulmonary edema occurred during induction of anesthesia but disappeared on continuous overatmospheric pressure ventilation and it was possible to proceed with the operation.

Three patients developed cardiac arrest during operation. Two of these had not received Arfonad. In them digital commissurotomy was quickly performed followed by intermittent cardiac compression. The result obtained was satisfactory in 1 case, but, in the other, Arfonad was given for an additional transventricular dilatation to enlarge the orifice still more. In the third case Arfonad may have been partly responsible for the cardiac arrest. The patient, a 49-year-old woman received 5+10+5 mg. of Arfonad and a drop in blood pressure to 30 mm. Hg occurred before the dilatation. All 3 patients were revived with a good result.

One patient having transventricular dilatation, without Arfonad, performed at a systolic blood pressure of 160 mm. Hg, had considerable bleeding from the left ventricle. In this case a total dose of 50 mg. of Arfonad was given after the dilatation, reducing the blood pressure to 80, thus greatly facilitating closure of the left ventricular incision. This instance gave the impetus to the routine use of Arfonad.

Additional Surgery: Embolectomy had to be performed in connection with the dilatation in 2 patients. Tracheostomy with postoperative prolonged artificial ventilation was performed in 8 cases.

One patient had a decortication and another a total gastrectomy performed in addition to the mitral operation.

In 1 patient, a thin-walled left ventricular aneurysm was found near the apex. There was a systolic bulging of the aneurysm which, after commissurotomy, was enlarged to a diameter of 2 cm. A row of heavy mattress silk sutures placed through strips of pericardium on each side of the aneurysm made the paradoxical movements disappear. The patient made an uneventful recovery.

TABLE III. THE OPENING IN THE MITRAL ORIFICE OBTAINED AFTER THE COMMISSUROTOMY, COMPARING THE DIGITAL (60 CASES) WITH THE TRANSVENTRICULAR DILATATION (83 CASES) TECHNIQUE*

SIZE OF MITRAL OPENING AFTER OPERATION	DIGITAL COMMISSUROTOMY (NO. OF CASES)	TRANSVENTRICULAR DILATATION (NO. OF CASES)
4 cm. (2 fingers)	7	37
3½ cm. (1¾ fingers)	6	13
3 cm. 1½ fingers)	30	29
2½ cm. (1¼ fingers)	14	4
2 cm. (1 finger)	3	0
Totals	60	83

*The mitral opening was calculated by the same surgeon's index finger and the greatest diameter calculated in centimeters where 1 fingerbreadth corresponds to 2 cm.

The Size of the Opening Obtained.—The size of the opening obtained after a transventricular dilatation has been significantly greater than that after digital commissurotomy (Table III).

Regurgitation.—When evaluating the regurgitation complicating the transventricular method, we observed a greater number of regurgitations of smaller degree than when the digital commissurotomy was performed. However, we encountered 4 cases in which an insufficiency was improved after transventricular regurgitation, which never occurred after digital commissurotomy Table IV).

TABLE IV. A COMPARISON OF THE REGURGITATION PRODUCED BY DIGITAL COMMISSUROTOMY (60 CASES) AND THE TRANSVENTRICULAR COMMISSUROTOMY (83 CASES)*

REGURGITATION	DIGITAL COMMISSUROTOMY (NO. OF CASES)	TRANSVENTRICULAR DILATATION (NO. OF CASES)
Unchanged		
without insufficiency	41 } 56	51 } 65
with insufficiency	15 }	14 }
Increased		
2-3 cm.	2	2
1 cm.	2	12
Decreased		
2-3 cm.	0	2
1 cm.	0	2
Totals	60	83

*The insufficiency was calculated by a careful evaluation of how far behind the ostium the same surgeon could palpate the regurgitant jet before and after the commissurotomy.

Pressure Measurements.—Pressure measurements in the left atrium immediately before and after commissurotomy have only been performed in 18 cases. In 5 of these a significant pressure drop of more than 15 mm. Hg was obtained. There was no significant pressure change in 9 cases, and an increase in pressure of 6 mm. Hg in 1 case in which a regurgitation, palpable 2 cm. behind the mitral orifice, occurred after digital commissurotomy.

DISCUSSION

The transventricular dilatation of a mitral stenosis gives the largest opening, is the easiest and quickest method available and the only practical method in a case of reoperation or in the presence of a thrombosed auricular appendix. The counterpressure on the commissures by the dilator can be effected with less injury to the heart than by digital commissurotomy. It is recommended that the dilator should not be opened more than 3.5 cm. in a small heart. Therefore, the screw regulating the distance between the two branches of the dilator is adjusted after the size of the mitral ring has been estimated by palpation. If too much dilatation is performed, a tear in the annular attachment of the anterior leaflet followed by severe regurgitation may result.

Mortality and complications are not increased with the transventricular dilatation method. The short period of controlled hypotension has greatly

facilitated the procedure, especially the closure of the incision in the left ventricle. The use of Arfonad has not increased mortality or complications but has diminished the blood loss. Compared with the single intravenous dose used in "non-heart cases,"[8] the dose in cases of mitral stenosis must be much less. This certainly depends on the inability of the diseased heart to compensate for even the slightest decrease in peripheral resistance by an increase in cardiac output. On the other hand, as soon as the stenosis of the mitral valve is removed, the slight degree of ganglion block achieved by the doses of Arfonad used is easily compensated for by an increase in cardiac output. This may explain why, in most cases, there has been such a rapid spontaneous return to normal blood pressure after the dilatation. In no patients, except the ones with cerebral embolism, have we had any signs of postoperative cerebral damage.

In conclusion, we recommend the transventricular dilatation in every case of mitral stenosis without first making an attempt at digital commissurotomy.

In regard to cases of acquired aortic stenosis with a significant pressure gradient, we have an increased mortality rate and a high incidence of aortic insufficiency. At present, therefore, we perform an open operation with extracorporeal circulation in these cases.

SUMMARY

An analysis of the surgical techniques used in 150 cases of mitral stenosis is presented. Transventricular dilatation is compared with digital commissurotomy. The much larger opening obtained by the transventricular dilatation has made us prefer this technique in spite of a slightly higher incidence of regurgitation. The controlled hypotensive technique has facilitated the procedure, especially the closure of the left ventricle.

REFERENCES

1. Bailey, C. P.: The Surgical Treatment of Mitral Stenosis (Mitral Commissurotomy), Dis. Chest. **15**: 377, 1949.
2. Cooley, D. A., and Stoneburner, J. M.: Transventricular Mitral Valvotomy, Surgery **46**: 414, 1959.
3. Dubost, C., and Blondeau, P.: Les commissurotomies mitrales difficiles, J. chir. **72**: 5, 1956.
4. Gray, T. C., and Riding, J. E.: Anaesthesia for Mitral Valvotomy, Anaesthesia **12**: 129, 1957.
5. Harken, D. E., Ellis, L. B., Ware, P. F., and Norman, L. R.: The Surgical Treatment of Mitral Stenosis. I. Valvuloplasty, New England J. Med. **239**: 801, 1948.
6. Holmgren, A.: Circulatory Changes During Muscular Work in Man, Scandinav. J. Clin. & Lab. Invest. **8**: 1, 1956.
7. Logan, A.: The Transventricular Route for Mitral Valvulotomy, Kardiologia Polska **1**: 49, 1957.
8. Voorhoeve, H. C.: Controlled Hypotension in Gynaecology, Proceedings World Congress of Anesthesiologists, Scheveningen, Holland, Minneapolis, 1956, Burgess Publishing Company, p. 191.

STUDIES DURING PROLONGED EXTRACORPOREAL CIRCULATION

Report of a Four-Hour Perfusion in a Patient

Murray N. Andersen, M.D., Buffalo, N. Y.*

WITH the increased use of pump-oxygenators, attention has been focused upon the physiologic and biochemical changes during extracorporeal circulation. Certain abnormalities have been noted to occur during inadequate perfusion, notably total body hypoxia,[1, 5, 7] decreased renal function,[8] decreased liver function,[2] and metabolic acidosis with an increase in lactic acid levels.[5, 6, 7] These changes appear to be largely avoidable, at least for short periods of perfusion, by employment of adequate flow rates with well-oxygenated blood.

Certain changes in the blood constituents have also received considerable attention as actual or potential hazards, including destruction of red cells with liberation of free plasma hemoglobin, diminution in platlets and fibrinogen, and possible loss of other clotting factors leading to abnormalities in blood clotting.[4]

Most observations on the above-noted conditions have been obtained from brief perfusions, usually of 30 minutes or less, and rarely exceeding 1 hour. In a recent case, total body perfusion with a pump-oxygenator was performed in a 9-year-old boy for slightly more than 4 hours due to an uncorrectable abnormality. Serial laboratory determinations performed before and during perfusion in this patient provided an unusual opportunity to assess the extent of changes occurring during prolonged total body perfusion and to determine whether such changes are progressive with time or self-limiting. The physiologic and biochemical responses are significant, not only in assessing the safety of prolonged perfusion, but in evaluating more accurately the probabilities of abnormalities developing during shorter periods of extracorporeal circulation.

CASE REPORT

R. C., a 9-year-old boy, was admitted to the hospital on May 8, 1959. The patient had had a known heart murmur since birth with recent exertional dyspnea and anterior chest pain. Chest x-ray studies showed left ventricular enlargement with increase in size during the 2 years prior to this admission. Electrocardiograms indicated left ventricular strain.

From the Department of Surgery of the University of Buffalo School of Medicine and the Edward J. Meyer Memorial Hospital, Buffalo, N. Y.

This study was supported in part by a grant from the U. S. Public Health Service (H-3720) and in part by a grant from the Erie County Heart Association.

Received for publication Feb. 1, 1960.

*Markle Scholar in Medical Science.

Retrograde catheterization revealed a pressure within the left ventricle of 190/80 mm. Hg and in the ascending aorta of 90/60 mm. Hg, with a withdrawal pattern indicating a subvalvular aortic stenosis lying 2 to 3 cm. below the valve.

On May 13, 1959, thoracotomy was performed through a sternal splitting incision. The left ventricle was greatly enlarged externally and thick walled, with barely visible contractions during systole. A coarse thrill was palpable at the root of the aorta. After the necessary cannulation, including provision for decompression of the pulmonary circuit, perfusion was begun and a vertical aortotomy was performed. Excellent visualization was obtained, disclosing a normal-appearing aortic valve and no localized obstruction down to the limit of visibility. Digital exploration revealed a small left ventricular chamber due to enormous thickening of the ventricular wall and septum, but no localized obstruction could be palpated. The aortotomy was repaired and the ascending aorta released.

Shortly after the original occlusion of the ascending aorta, ventricular fibrillation developed and continued throughout the period of aortic occlusion, which lasted 21 minutes. After perfusion of the heart was resumed, defibrillation was accomplished with an electric shock of 200 volts for 0.5 second. Good contractions were evident in the right ventricle, with the left ventricle resuming its previous type of barely visible contractions. The extracorporeal flow rate was reduced and then discontinued. The systemic arterial pressure immediately fell rapidly and the venous pressure rose, with the heartbeat becoming progressively weaker; perfusion was resumed promptly. During the succeeding 3 hours and 50 minutes, several attempts were made to discontinue the extracorporeal circulation, but in each instance there was a rapid weakening of the heartbeat with a fall in arterial blood pressure and rise in venous pressure, necessitating prompt restitution of perfusion. Several drugs were administered intravenously without benefit in terms of effective cardiac action, including digitalis, calcium, noradrenalin, and Vasoxyl.

At the end of 4 hours and 10 minutes of extracorporeal circulation, perfusion was withdrawn and the patient died shortly thereafter with rapid and progressive left ventricular failure.

Autopsy disclosed idiopathic left ventricular and septal hypertrophy of a very advanced degree. No localized outflow obstruction was present and the remainder of the heart was normal.

OBSERVATIONS DURING PERFUSION

Technique.—Total body perfusion was performed using a Crafoord-Senning pump-oxygenator. The extracorporeal circuit was primed with 2,100 c.c. of donor blood which had been collected 4 hours prior to beginning perfusion in silicone-coated bottles containing 20 mg. of heparin in 15 c.c. normal saline. No additional blood was added to the machine or transfusions given during the entire period of perfusion.

Flow Rate and Arterial and Venous Pressures.—A total flow of approximately 2,000 ml./min. (70 ml./Kg./min.) was anticipated; immediately after initiation of perfusion, flow increased to 2,500 ml./min. (83 ml./Kg./min.) and this average flow rate was maintained for the remainder of perfusion.

Prior to initiation of perfusion, the patient's aortic blood pressure averaged 120/70 mm. Hg. Immediately following the beginning of perfusion, the pressure dropped to 70/50 and subsequently rose to the range of 90-120/70-90 mm. Hg. With each cessation of perfusion, the arterial pressure fell rapidly over a period of 1 to 2 minutes to approximately 40/30 mm. Hg.

The venous pressure during the control period averaged 10 cm. H_2O. Immediately after beginning extracorporeal circulation the central venous

pressure fell to approximately 4 cm. H_2O and remained in this range throughout the duration of perfusion. With each cessation of perfusion, accompanying the rapid fall in systemic arterial blood pressure, the inferior vena caval pressure rose rapidly within 1 to 2 minutes to the range of 22 cm. H_2O.

In each instance after restitution of total perfusion, the arterial and venous pressures reverted immediately to the previous levels.

No gross change in peripheral resistance, as indicated by the relation of blood flow to arterial pressure, was evident throughout the period of extracorporeal circulation.

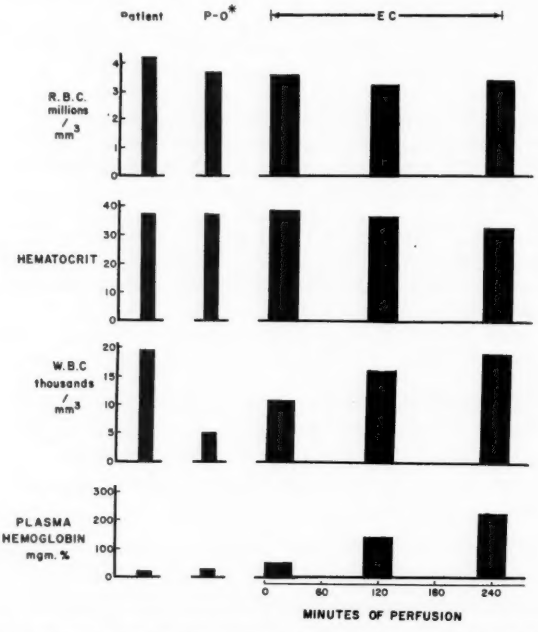


Fig. 1.—Observations on the cellular elements of the blood. P-O* = Pump-oxygenator; samples in this column were drawn from the pooled donor blood after the pump-oxygenator was primed.

Cellular Elements of the Blood (Fig. 1).—During the period of perfusion the red cell count showed a slight decrease and the hematocrit fell from 38 per cent to 32 per cent.

The white cell count during perfusion rose from 12,200 to 18,150, slightly below the patient's pre-perfusion level. This change was primarily due to an increase in the nonsegmented polymorphonuclear leukocytes.

Free plasma hemoglobin levels increased progressively, reaching a final level of 255 mg. per cent. A large proportion of this increase in plasma hemoglobin may have been produced by the aspiration system which was in use more or less continuously.

Acid-Base Balance and Oxygen Consumption (Fig. 2).—The initial pH determination from the patient was 7.45. During the first 1½ hours of

perfusion, the pH decreased to 7.18 and at this point 5 Gm. of $NaHCO_3$ was administered intravenously. During the subsequent 2½ hours of perfusion, the pH remained constant at 7.3.

The pCO_2 ranged from 22 to 29 mm. Hg in the venous blood and from 20 to 23.5 mm. Hg in the arterialized blood. Since no carbon dioxide was used in the oxygenating gas, this low carbon dioxide tension is predictable, tending to produce some correction of any tendency toward acidosis.

The plasma bicarbonate decreased from 16 mEq./L. in the venous blood at the beginning of perfusion to 10.5 mEq./L. after 1½ hours. Following the administration of $NaHCO_3$, the level rose to 13 mEq./L.

The oxygen consumption during perfusion increased from 3.5 ml./Kg./-min. to 4.7 ml./Kg./min.

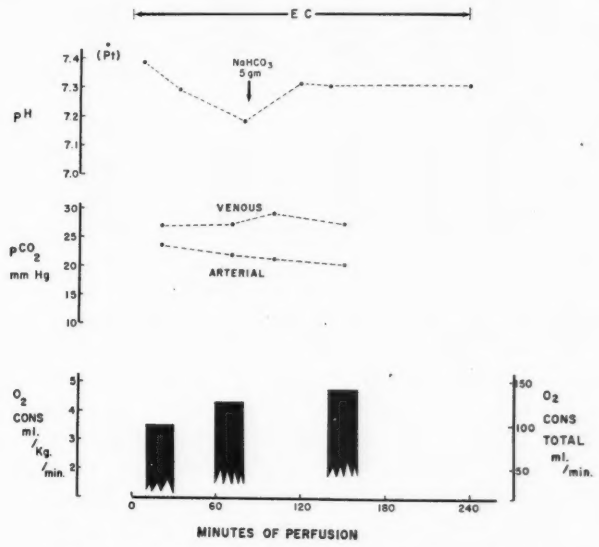


Fig. 2.—Acid-base balance and oxygen consumption.

Blood Clotting Factors (Fig. 3).—The platelet count fluctuated somewhat, with an initial level of 174,000 and a final level of 141,000 at the conclusion of perfusion.

The fibrinogen level showed a slight decrease during perfusion from an initial value of 275 mg. per cent to a final level of 210 mg. per cent.

Indirect information on other clotting factors was obtained from the serial protamine titrations performed during the perfusion. At the end of 4 hours of perfusion, the blood clotted in a normal time in the test tubes to which appropriate amounts of protamine were added. The clots were firm, clot retraction was good, and there was no evidence of fibrinolytic activity either at room temperature or after incubation at 37° C. for 24 hours.

Active Heparin Levels During Perfusion (Fig. 4).—An initial dose of 2.5 mg./Kg. of heparin was administered prior to cannulation for perfusion, producing an interpolated level of approximately 18 to 19 γ/ml. During the subsequent 2 hours and 20 minutes, this decreased steadily to 7.5 γ/ml. At this point, 1.0 ml./Kg. of heparin was added. One hour and 40 minutes later, the active heparin level had decreased to 5 γ/ml. At this time it was noted that free blood which was allowed to lie in the wound for a period of time was beginning to clot. Heparin, 2.0 mg./Kg., was then added with an increase in the active heparin level to 22 γ/ml.

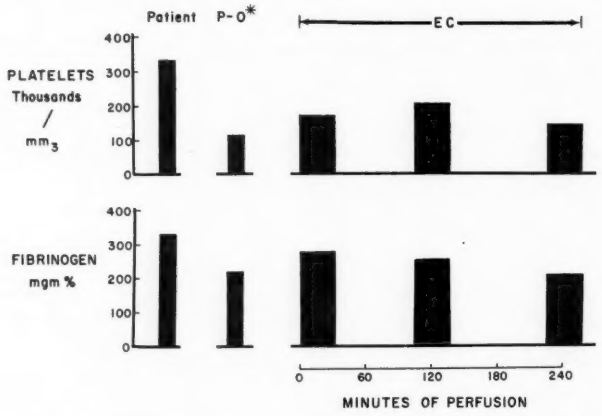


Fig. 3.—Clotting elements. P-O* = Pump-oxygenator; samples in this column were drawn from the pooled priming blood in the pump-oxygenator prior to beginning perfusion.

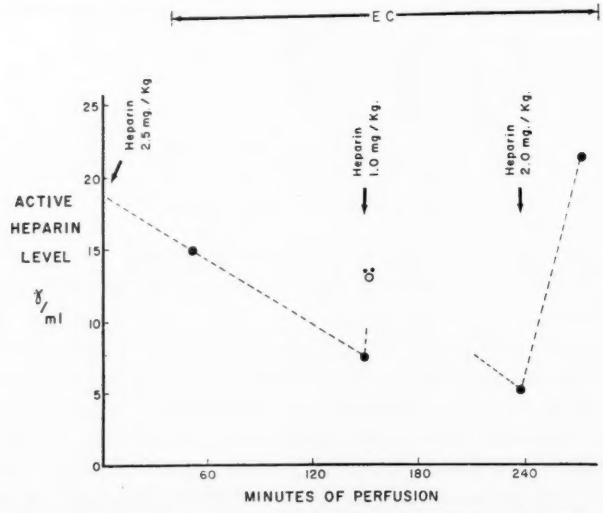


Fig. 4.—Active heparin levels as determined by serial protamine titrations. The active heparin level was estimated from the amount of protamine per milliliter required to produce a normal clotting time, assuming an inactivation ratio of 1:1. The point "O" was interpolated from the inactivation rate observed during the first 2½ hours of perfusion.

DISCUSSION

In evaluating the biochemical effects of perfusion, it is essential to consider the adequacy of perfusion and the apparatus used, since the degree of trauma to the blood cannot reasonably be expected to be identical with varying types of oxygenators and pumps. In this case the perfusion rate was thought to be satisfactory, 70 to 85 ml./Kg./min., and the total body oxygen consumption would appear to be adequate for an anesthetized patient, ranging from 3.5 to 4.8 ml./Kg./min. However, during the intermittent attempts to discontinue perfusion, there was a rapid drop in circulatory rate and blood pressure, with evidence of hypoxia and acidosis, as manifested by the characteristic heaving ventilatory efforts of the patient; these subsided promptly with re-institution of perfusion. It is probable that these periods of transient hypoxia contributed materially to the drop in pH which occurred at one point. Subsequently, when the perfusions were maintained longer between attempts at discontinuance, the pH remained stable. The increased elimination of CO_2 during perfusion could be expected to provide some compensation for a certain degree of metabolic acidosis.

In general, the blood constituents measured showed little significant change during the perfusion. The levels at the beginning of perfusion reflected the respective levels of these elements in the priming blood and the patient's blood and the decreases observed initially appeared to be largely attributable to the low concentrations in the donor blood, particularly in platelets and fibrinogen. The most striking change which occurred during perfusion was in the white blood cell count which showed a rapid and progressive increase, although the terminal value was still slightly less than the level in the patient prior to perfusion. There was no evidence of hemoconcentration due to dehydration of the blood from continual exposure to the gaseous atmosphere in the oxygenator and the slight hemodilution which occurred is probably accountable on the basis of intravenous infusion of fluids during the prolonged procedure.

The increase in free plasma hemoglobin was not excessive and the final value after 4 hours was well below what would commonly be considered a dangerous level. A substantial proportion of the free hemoglobin accumulation may have been due largely to the intermittent but frequent use of the aspirator with its attendant foaming, since previous studies have indicated that the rate of hemolysis with this pump-oxygenator is considerably less than that observed.

Considerable attention has been devoted to blood coagulation changes occurring during perfusion.[4] The blood in the present case showed an adequate level of platelets and fibrinogen at the end of perfusion and the integrated clotting time, as indicated with addition of protamine, appeared to be normal. Since protamine does not replace or supplement clotting factors and appears to have no significant affect on blood clotting other than the neutralization of heparin, this would appear to be evidence of adequate residual levels of the essential clotting factors. The normal clot retraction and the absence of fibrinolytic activity tend to support this view.

The rate of heparin inactivation observed during perfusion agreed rather well with previous experimental studies[3] and introduced a point of practical significance. During the period at which the active heparin level fell below 10 γ/ml., formation of soft clots was observed in blood which lay in the wound for a period of time and it is probable that some precipitation of fibrin may have occurred during this period, accounting for the observed slight decrease in fibrinogen levels. However, no depositions of fibrin were grossly observable in the pump-oxygenator at the conclusion of the procedure. This decrease in the active heparin level has prompted us routinely to obtain samples for titration from the pump-oxygenator every 30 minutes during perfusion to avoid the danger of clotting. Theoretically, from the observed rate of inactivation one could calculate the amount of heparin which would need to be added at intervals during perfusion if a single titration were performed at the beginning of perfusion and if the inactivation rate during perfusion could be predicted with certainty. However, until further documentation of the rate of change is obtained, it is thought to be a safer procedure to repeat the titrations at intervals throughout perfusion.

The over-all picture in the parameters measured was one indicating the maintenance of a relatively stable state. The evidence that the lowered levels of the various constituents noted during perfusion is largely a result of the low concentrations found in donor blood suggests that development of better methods of collecting and preserving blood prior to use would increase the margin of safety even further.

SUMMARY

A case has been reported in which a patient underwent total body perfusion with an artificial pump-oxygenator for over 4 hours. The decreased levels of the certain blood constituents in the early stages of perfusion appeared to be the results of the proportions of these elements in the patient's blood and in the pooled donor blood used for priming the pump-oxygenator.

During the period of perfusion the following observations were made.

1. The red blood count and hematocrit decreased slightly.

2. The white blood count showed a substantial and progressive increase, largely in nonsegmented polymorphonuclear leukocytes.

3. The platelet count varied somewhat with the final level showing a slight decrease.

4. The fibrinogen level decreased slightly.

5. The pH showed an early decrease which was corrected by administration of intravenous sodium bicarbonate. It remained constant during the final 2½ hours of perfusion.

6. Evidence was not found for change in peripheral resistance nor expansion in capacity of the vascular bed during perfusion. With quantitative aspiration of blood loss in the operative field, it was not necessary to add blood beyond the original priming volume of the pump-oxygenator.

7. The active heparin level decreased rapidly during perfusion, necessitating periodic infusion of additional amounts of heparin to prevent clotting in the system.

8. Addition of protamine to the blood at the end of perfusion produced satisfactory blood coagulation. Clot retraction was normal and there was not evidence of fibrinolytic activity.

9. Free plasma hemoglobin did not increase to dangerous levels, despite the prolonged use of the blood aspirator.

REFERENCES

1. Andersen, M. N., and Senning, Å.: Oxygen Consumption During Extracorporeal Circulation With a Pump-Oxygenator, Ann. Surg. **148**: 59, 1958.
2. Andersen, M. N., and Senning, Å: Studies of Liver Function During Extracorporeal Circulation With Low Flow Rate, Surgery **43**: 397, 1958.
3. Andersen, M. N., Mendelow, M., and Alfano, G.: Experimental Studies of Heparin-Protamine Activity With Especial Reference to Protamine Inhibition of Clotting, A. M. A. Arch Surg. **79**: 542, 1959.
4. Brown, I. W., Jr., and Smith, W. W.: Hematologic Problems Associated With the Use of Extracorporeal Circulation for Cardiovascular Surgery, Ann. Int. Med. **40**: 1035, 1958.
5. Clowes, H. A., Jr., Neville, W. E., Sabga, G., and Shibota, Y.: The Relationship of Oxygen Consumption, Perfusion Rate, and Temperature to the Acidosis Associated With Cardiopulmonary Circulatory Bypass, Surgery **44**: 220, 1958.
6. Crafoord, C., Norberg, B., and Senning, Å.: Clinical Studies in Extracorporeal Circulation With a Heart-Lung Machine, Acta chir. scandinav. **112**: 220, 1957.
7. Reed, W. A., and Kittle, C. F.: Survival Rate and Metabolic Acidosis After Prolonged Extracorporeal Circulation With Total Cardiopulmonary By-pass, Ann. Surg. **148**: 219, 1958.
8. Senning, Å., Andres, J., Bornstein, P., Norberg, B., and Andersen, M. N.: Renal Function During Extracorporeal Circulation at High and Low Flow Rates, Ann. Surg. **151**: 63, 1960.

RENAL ARTERIOGRAPHY DURING EXTRACORPOREAL CIRCULATION IN DOGS, WITH A PRELIMINARY REPORT UPON THE EFFECTS OF LOW MOLECULAR WEIGHT DEXTRAN

Walter Finsterbusch, M.D., David M. Long, M.D., Robert D. Sellers, M.D., Kurt Amplatz, M.D., and C. Walton Lillehei, M.D., Minneapolis, Minn.*

KIDNEY complications during and after extracorporeal circulation have proved to be relatively common in human beings in total bypass periods exceeding 1½ hours and in experimental animals. Such factors as hypotension and/or high levels of plasma hemoglobin are known to predispose to renal complications but we have been impressed by their occurrence in instances where the arterial blood pressure was never low and the plasma hemoglobin was consistently low. An attempt was made, therefore, to study the changes in the renal artery occurring during extracorporeal circulation by aortorenal arteriography in 10 dogs.

METHODS

Twelve adult mongrel dogs of both sexes, weighing between 9 and 15 kilograms, were anesthetized with 2.5 per cent thiopental sodium given intravenously. The animals were prepared for cardiopulmonary bypass, utilizing a disposable unitized plastic sheet oxygenator and a Sigmamotor pump, as previously described.[1, 2] A median incision with medial sternal split was made contrary to our previous method.[1, 2] Following heparinization of the animals with 3 mg. of heparin per kilogram, the femoral artery was cannulated by a plastic arterial catheter, Bardic No. 12-14, depending on the size of the artery. In 3 animals the left subclavian artery was used instead of the femoral. The venous return was collected by the cannulation of the right atrium and right ventricle with the use of a No. 40 Bardic plastic catheter. A snare of umbilical tape was placed around the great vessels through the transverse sinus so that the base of the pulmonary artery could be occluded. The other femoral artery

From the Departments of Surgery and Radiology, University of Minnesota Medical School, Minneapolis, Minn.

Supported by research grants from the Graduate School, University of Minnesota; Minnesota Heart Association; Life Insurance Medical Research Fund; National Heart Institute, U. S. Public Health Service (No. H-830), and the University of Minnesota Cardiac Research Fund.

Received for publication Feb. 1, 1960.

*Present address: Department of Surgery, Graz University, Graz, Austria.

was used to insert a polyethylene catheter, ranging from PE 240 to 280, depending on the size of the artery. The arteriography catheter had a closed end and several side holes. Its tip was placed, under fluoroscopic control, at the level of the renal arteries. Before venous cannulation, a control arteriogram was made using 5 c.c. of 90 per cent Hypaque and 2 c.c. of saline solution. Two roentgenograms were obtained during the arterial and nephrographic phases. The arterial phase roentgenogram was exposed just as the injection of contrast medium was completed and the nephrogram was made approximately 5 to 10 seconds later. After cardiopulmonary bypass was started, the previously described snare was tightened, obstructing the pulmonary artery but not the aorta. Renal arteriograms were obtained at 30-minute intervals up to 2 hours. After 2 hours of continuous extracorporeal circulation, 2.5 mg. per kilogram of body weight of hexamethonium bromide was injected intra-arterially in the animals of Groups I, II, and III. Fifteen minutes after the injection of this substance, the final renal arteriogram was obtained. The animals in Group III had 500 c.c. of low molecular weight dextran (10 per cent solution added to the oxygenator priming blood). The perfusion rate of 60 c.c. per kilogram of body weight per minute was kept constant in each animal. The oxygenation was kept constant as well, using 3 L. of 100 per cent oxygen per minute per liter of blood flow. Before each renal arteriogram, pressures were recorded through the polyethylene catheter using a standard pressure transducer and recording device. Two animals were used as controls without extracorporeal circulation to assess the possibility of arterial changes caused by other factors.

The examined animals with extracorporeal circulation were divided into three groups.

Group I.—Total extracorporeal circulation for 2 hours and 15 minutes by cannulation of the left femoral artery in 4 animals.

Group II.—Same type and duration of extracorporeal circulation using the left subclavian artery in 3 dogs.

Group III.—Same type and duration of extracorporeal circulation by cannulation of the left femoral artery and priming of the sheet oxygenator with 500 c.c. of low molecular weight dextran* solution,[4, 8] in addition to 1,000 c.c. of heparinized blood. (In Groups I and II, 1,500 c.c. of heparinized blood were used for priming of the sheet oxygenator.)

RESULTS

In Group I significant roentgenographic changes of the renal arteries were observed just after starting the extracorporeal circulation in 3 of the 4 animals. These changes consisted of diffuse narrowing and straightening of the main renal arteries and a rather marked "thready" appearance of the intrarenal arterial branches. The angle of the take-off of the renal arteries from the aorta was changed due to marked straightening of the main renal

*The low molecular dextran utilized was: dextran fraction FDR 858, 10 Gm.; Na Cl. 0.9 Gm.; and sterile water, ad 100 ml. Intrinsic viscosity = 0.19. The average molecular weight was 31,000 with a range from 21,000 to 41,000.

arteries. The intraparenchymal renal arteries appeared straight as compared with the control renal arteriogram obtained before the extracorporeal circulation was started. In addition to these apparently diffuse arterial changes, the nephrographic effect was considerably diminished. In spite of good opacification of the aorta, there was relatively poor staining of the renal arteries (Figs. 1 and 2). The described changes, however, improved after ½ to 1 hour of pump run. However, straightening and narrowing of the intraparenchymal

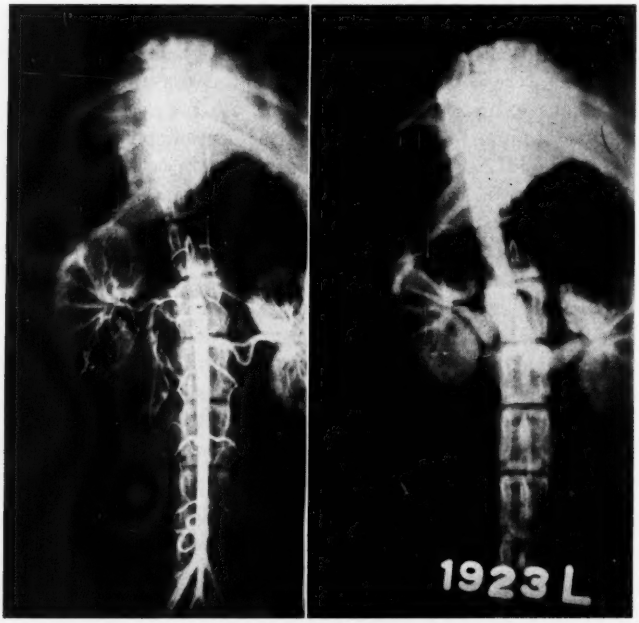


Fig. 1.—Dog No. 1923–Control renal arteriogram made after anesthesia and cannulations but before starting extracorporeal circulation. On left is the arterial phase and on right is the venous (nephrogram) phase. The important features to be noted in the arteriogram are the excellent opacification of the cortex, the tortuous course of the extrarenal and main intrarenal vessels in the medulla. The nephrogram shows good opacification.

arteries was still clearly present (Fig. 3). After 2 hours, there was no significant change in the appearance of the renal arteries, although the nephrogram seemed to be improved. The nephrograms, however, were not as good as those obtained just prior to extracorporeal circulation (Fig. 4). No improvement was noted following the intraarterial injection of hexamethonium. In 1 animal in Group I there were no significant roentgenographic changes in the appearance of the main or intraparenchymal renal arteries.

In Group II (perfusion through the left subclavian artery), in 1 animal the same roentgenographic changes were observed as described in 3 of the animals in Group I (Figs. 5 and 7). In the other 2 animals, the renal vascular changes were minimal with only questionable narrowing of the renal arteries, appearing just after going on the pump. In this group, also, there was no change following the injection of hexamethonium bromide intra-arterially.

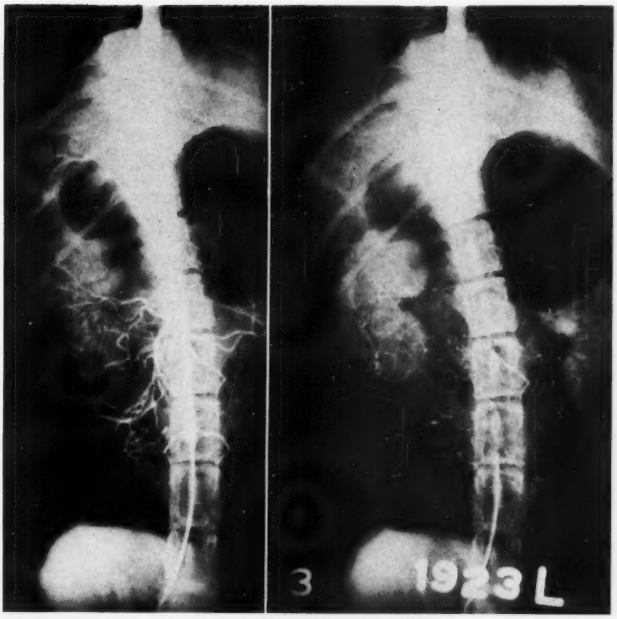


Fig. 2.—Dog No. 1923–Thirty minutes after starting extracorporeal circulation with retrograde femoral arterial perfusion. Note the poor cortical staining, the straightened and narrowed extrarenal and main intrarenal arteries. The nephrogram shows pale staining.

Fig. 3.—Dog. No. 1923–Sixty minutes after starting extracorporeal circulation. Note improvement in the caliber of the arterial vessels, no change in course, and no improvement in cortical opacification nor in the nephrogram.

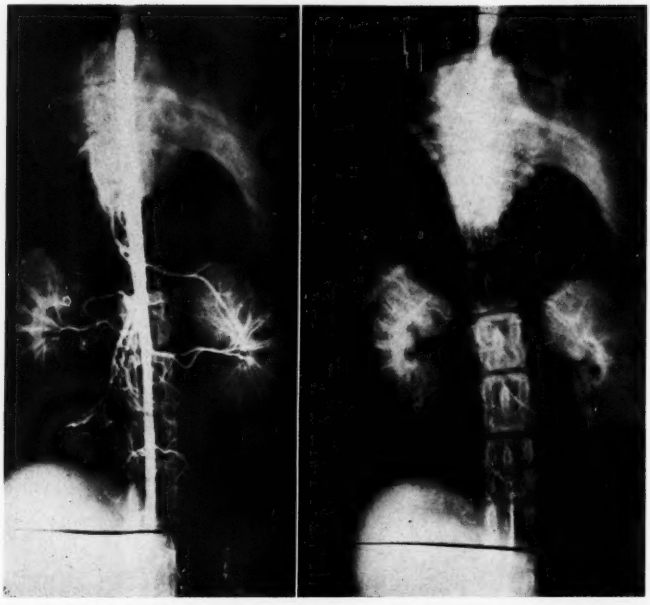


Fig. 4.—Dog No. 1923–Two hours after starting extracorporeal circulation. Conditions here are now similar to those shown in Fig. 2. In the nephrogram, good concentration of contrast medium is seen. The ureters and the much enlarged urinary bladder are also well opacified.

Fig. 5.—Dog No. 550–Control renal arteriogram before starting extracorporeal circulation utilizing subclavian artery catheter for perfusion. Note similarity to Fig. 1.

Fig. 6.—Dog No. 550–Thirty minutes after starting extracorporeal circulation. All changes are similar to those shown in Fig. 2.

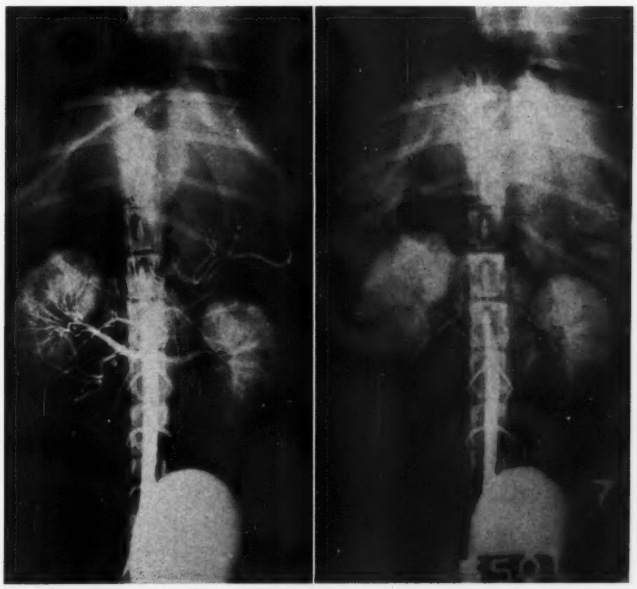


Fig. 7.—Dog No. 550–Two hours after starting extracorporeal circulation. Notice the good nephrogram effect. Here the cortical opacification appears to be improved and the main intrarenal arteries show better filling but are narrowed. The extrarenal vessels are still stretched out.

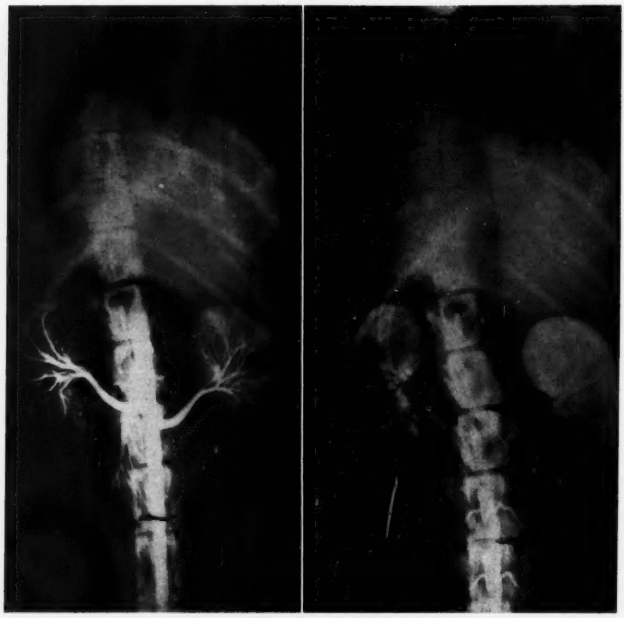


Fig. 8.—Dog No. 916–Control renal arteriogram before extracorporeal circulation utilizing femoral artery cannulation and 500 ml. low molecular weight dextran. Note similarity to Figs. 1 and 5.

Fig. 9.—Dog No. 916–Thirty minutes after starting extracorporeal circulation. Note the absence of any significant changes.

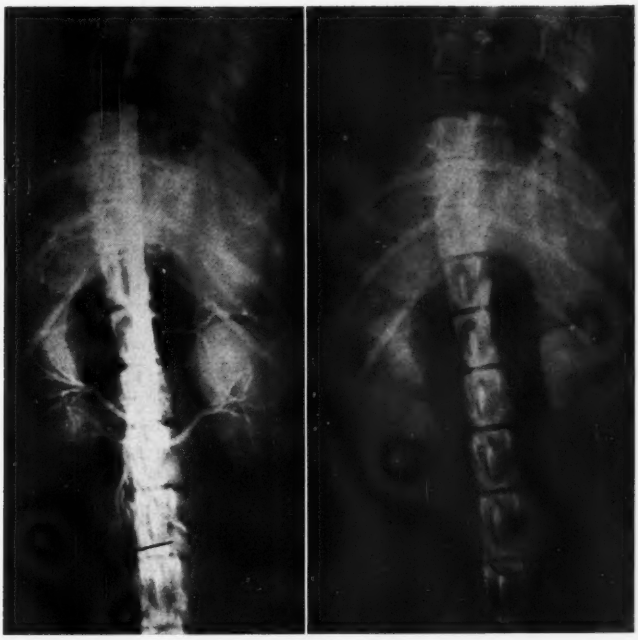


Fig. 10.—Dog No. 916–Ninety minutes after starting extracorporeal circulation. Significant changes from the control have now appeared in the renal circulation.

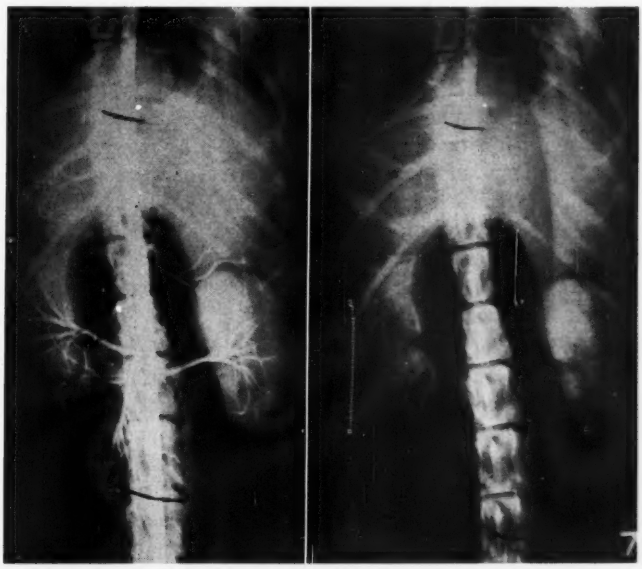


Fig. 11.—Dog. No. 916–Two hours after starting extracorporeal circulation. Notice the good nephrogram effect. However, the characteristic changes of absent cortical filling and straightened and narrowed main renal vessels are now well developed in the arteriogram.

In Group III (perfusion through femoral artery with low molecular weight dextran added), the appearance of the renal arteries remained normal in all three studies during the first ½ hour of extracorporeal circulation (Figs. 8 and 9). After 1 hour, there was narrowing and straightening of the renal arteries which increased after 1½ hours. The intrarenal arteries appeared "thready" (Fig. 10). In 2 of the dogs, the nephrographic effect was judged to be normal, and in 1 dog it was thought to be decreased after 1½ hours. The most severe changes were seen after 2 hours of continuous extracorporeal circulation (Fig. 11). Again, in this group, there was no improvement following the injection of hexamethonium bromide.

DISCUSSION AND COMMENTS

These experiments showed changes in the vessels of the kidneys during extracorporeal circulation which may explain disturbances in the renal function after cardiopulmonary bypass. The experiments of Trueta and his co-workers[3] have shown that injuries produced by placing a tourniquet around one hind limb may cause changes in the renal circulation. These changes could be prevented by division of the splanchnic nerves. With extracorporeal circulation, the femoral artery is frequently used for cannulation and the arterial catheter is fixed with a snare around the artery. These preliminary studies have also revealed more severe changes, in 3 of 4 dogs in the arteries of the kidney, with the use of the femoral artery for cannulation during extracorporeal circulation than with the subclavian artery. This finding may be related to the reversed direction of the blood flow in perfusions through the femoral artery.

Gelin[4] demonstrated that tissue injuries, such as burns and fractures, are followed by a disturbed suspension stability of the blood which leads to intravascular aggregation of red cells. This phenomenon is followed by decreased capillary flow and morphologic tissue changes which are distant to the site of injury. This same author, studying the circulation in the capillary bed of the bulbar conjunctiva by means of a dissecting microscope, also demonstrated that arterial spasm increased the severity of aggregation in the precapillary arterioles and stasis in the postcapillary venules. The morphologic changes arising from intravascular aggregation of red cells in the kidneys have been reported in another paper.[5] The intravascular aggregation of red cells with decreased capillary flow and morphologic tissue changes could be prevented by administering low molecular weight dextran.[4, 5]

It should be emphasized that there are distinct differences in the biologic effects of high and low molecular weight dextran solutions.[4] High molecular weight solutions decrease the suspension stability of the blood corpuscular elements thus increasing the sedimentation rate and promoting red cell aggregates. The low molecular weight preparation on the other hand increases the blood suspension stability, decreases the sedimentation rate, and diminishes or prevents red cell sludging. These properties, together with the fact that it constitutes an effective plasma expander and is an osmotic diuretic, have initiated this investigation into the possible value of low molecular weight dextran

solutions in extracorporeal circulation. Moreover, there is considerable interest in the use of deep hypothermia for cardiac surgery, either alone or combined with a pump-oxygenator, and there is a distinct possibility that many of the problems of deep hypothermia can, at least in part, be explained by a failure in capillary circulation due to sludging of red cells. Gelin and Lofstrom[9] have presented evidence that low molecular weight dextran solutions diminish this instability of blood at low body temperature and thereby improve the microcirculation.

The fact that certain blood changes in patients undergoing extracorporeal circulation exist[6, 7, 8] and that it was possible in these experiments, by using low molecular weight dextran for priming the oxygenator, to delay and lessen the vascular changes has enabled us to conclude that decreased suspension stability of the blood with intravascular aggregation of red cells is an important factor during cardiopulmonary bypass. On the basis of these studies and the work of Gelin and associates,[4, 5] it appears that arterial spasm and intravenous aggregation of the blood cells leading to tissue hypoxia of the kidneys may exist and may be the explanation for some cases of postoperative oliguria or anuria where there was no evidence of blood incompatibility, excessive hemolysis, or arterial hypotension.

CLINICAL APPLICATION

Since September, 1959, low molecular weight dextran has been utilized routinely in the priming volume of our pump-oxygenator. A 10 per cent solution of dextran in 0.9 per cent saline has been used. Two to four grams of dextran per kilogram of body weight has been the approximate dosage used. In 90 patients, many with bypass intervals exceeding 1½ hours, there has not been a single renal complication. Data previously collected[8] have indicated that the prevention of red blood cell aggregation in longer bypass intervals also has significant beneficial effects upon tissue perfusion of the liver, gastrointestinal tract, heart, and kidneys.

It is well known that high molecular weight dextran solutions may inhibit blood clotting. The effects of low weight solutions upon blood clotting are being intensively and broadly studied.* No conclusions have been reached as yet.

SUMMARY AND CONCLUSION

1. Striking changes of renal arteriograms made during extracorporeal circulation were observed.

2. These changes are not completely uniform and varied some from animal to animal.

3. These changes may be less prominent in perfusions through the left subclavian artery instead of the femoral artery.

*An important by-product of these studies has been the finding by Dr. Eugene Bernstein,[10] of this department, that premedication with low molecular weight dextran results in a remarkable increase in the safe dose tolerance for iodine-containing contrast media (90 per cent Hypaque) for cardioangiography thus indicating that red cell sludging is one of the important mechanisms responsible for its toxicity.

4. Hexamethonium bromide injected intra-arterially after 2 hours did not result in improvement of the radiographic picture.

5. The most prominent changes in the renal arteriograms were narrowing, straightening, and loss of the normal curvature of the renal arteries. The roentgenographic changes were more marked during the first ½ hour of extracorporeal circulation.

6. Administration of 500 c.c. of low molecular dextran solution delayed and lessened the described renal vascular changes.

We wish to express appreciation to Pharmacia, Uppsala, Sweden, for supplying the low molecular weight dextran solution.

REFERENCES

1. Gott, V. L., DeWall, R. A., Paneth, M., Zuhdi, M. N., Weirich, W. L., Varco, R. L., and Lillehei, C. W.: A Self Contained Disposable Oxygenator of Plastic Sheet for Intracardiac Surgery, Experimental Development and Clinical Application, Thorax **12**: 1, 1956.
2. Gott, V. L., Sellers, R. D., DeWall, R. A., Varco, R. L., and Lillehei, C. W.: A Disposable Unitized Plastic Sheet Oxygenator for Open Heart Surgery, Dis. Chest **32**: 615-625, 1957.
3. Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J., and Prichard, M. M. L.: Studies of the Renal Circulation, Oxford, 1948, Blackwell Scientific Publications.
4. Gelin, L. E.: Studies in Anemia of Injury, Acta chir. scandinav. Suppl. 210, 1956.
5. Fajers, C. M., and Gelin, L. E.: Kidney, Liver, and Heart Damages From Trauma and From Induced Intravascular Aggregation of Blood Cells. An Experimental Study, Acta path. et microbiol. scandinav. **46**: 97-104, 1959.
6. DeWall, R. A., Warden, H. E., Melby, J. C., Minot, H., Varco, R. L., and Lillehei, C. W.: Physiological Responses During Total Body Perfusion with a Pump-Oxygenator, Studies in 120 Patients Undergoing Open Cardiac Surgery, J. A. M. A. **165**: 1788-1792, 1957.
7. DeWall, R. A., Long, D. M., Gemmill, S. J., and Lillehei, C. W.: Certain Blood Changes in Patients Undergoing Extracorporeal Circulation, J. THORACIC SURG. **37**: 325-333, 1959.
8. Long, D. M., and Lillehei, C. W.: Effect of Low Molecular Weight Dextran Upon Physiologic Changes Induced by Total Body Perfusion From a Pump-Oxygenator. (To be published.)
9. Gelin, L. E., and Lofstrom, B.: A Preliminary Study on Peripheral Circulation During Deep Hypothermia, Acta chir. scandinav. **108**: fasc. 5, 1954.
10. Bernstein, E., and Evans, R.: Low Molecular Dextran: Its Protective Action Against Intravenous Hypaque Toxicity, Submitted for publication to Proc. Soc. Exper. Biol. & Med.

A METHOD FOR VASCULAR ANASTOMOSIS AND BYPASS INCLUDING APPLICATIONS

Edward I. Seltzer, M.D., Providence, R. I.

THE FUNDAMENTAL problem in vascular anastomosis is the maintenance of a normal arterial supply to the tissues involved during the period of corrective surgery. This paper describes the specific application of a technique, suggested originally by Johnson and co-workers,[2] in various regions including the aortic arch, the aorta, and many of the latter's great branches; but the general applicability of the technique is evident.

The method to be presented depends largely on the development of a simple, small, nontraumatic clamp which makes the technical phase of blood vessel anastomosis simple and permits a bypass that can be executed rapidly anywhere from the ascending aorta to the popliteal arteries. This clamp can also be used as a nontraumatic arterial occlusion clamp anywhere in the body. The unit can also be used in extracorporeal circulation complexes to hold and anchor all needles inserted into the vessels.

MATERIALS AND SUPPLIES

I. *The Clamp* (see Fig. 2).—It is essentially a short, stainless steel tube, one end being partitioned to form two slits to permit the introduction of a loop of umbilical tape (for very large blood vessels, a slightly larger clamp can be used and in place of the umbilical tape, one may use a shoelace). The other end of the tube is threaded and accommodates to a coupling of similar thread size. At the top of this coupling there is a swivel. This latter device prevents the umbilical tape which has been threaded through the tube from twisting and tearing when the clamp is tightened by counter-clockwise rotation of the coupling on the tube. Because of its circular grab on the host vessels the umbilical tape causes no damage to the intima. A specially devised long flat needle is used to thread the umbilical tape through the instrument.

II. *Materials* Used in Bypass Procedures.*—a. Polyvinyl tubing of various diameters. This material is relatively inert, strong, flexible, and can be fabricated and sterilized by the manufacturer into various sizes and shapes. It can also be fashioned in the operating room; any branch or joint so fashioned is firmly held, sealed, and actually welded in position by Plexitron cement.

Received for publication Feb. 3, 1960.
Address: 300 Pontiac Ave., Auburn 10, R. I.
*All these materials are supplied by the Baxter and Travelon Laboratories, Morton-Grove, Ill.

b. The needles or adaptors, fashioned into various sizes, are made of Implex (a synthetic resin). These adaptors can be firmly glued into the polyvinyl tubing with the Plexitron cement. Each needle has a small flange at its end. This prevents the possible slipping of the clamped structures.

The above materials when assembled in the operating room are cold sterilized by Warexin.*

The materials for use in the permanent graft are Teflon, Dacron, or a homograft.

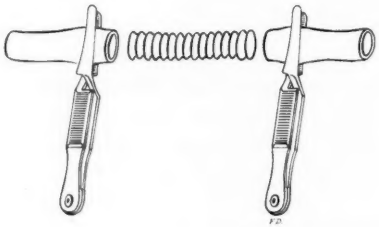


Fig. 1.—The conventional method of vascular anastomosis.

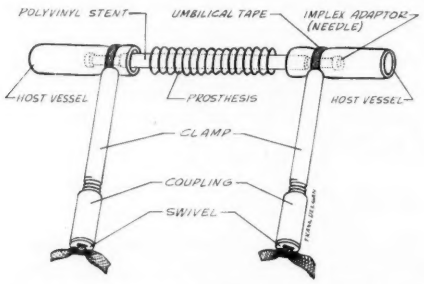


Fig. 2.—The proposed method of anastomosis, demonstrating the clamp, its method of application, and the bypass principle.

METHOD

Blood Vessel Anastomosis (see Fig. 1).—The figure depicts the conventional method of blood vessel anastomosis in its simplest form.

The proposed method in its simplest form (Fig. 2) is essentially a stent of polyvinyl tubing with an Implex adaptor at each end. This is passed through the permanent graft and then slid into the host arterial end (proximal and distal) and maintained in place by clamps. When these clamps are tightened with a few twists of the coupling on the metal tube, one has an immediate watertight conduit capable of carrying a heavy pressure load, and the anastomosis can now proceed with dispatch. It is easily executed, permitting the everting sutures to be evenly and accurately placed. The clamps are used as a lever to rotate the anastomotic line, and only the surgeon's hand is in the operative field. It is not necessary to preclot any of the synthetic grafts for, at the termination

*The Guardian Chemical Company, Long Island, N Y.

of both anastomoses, one of the clamps is slightly loosened. This permits some blood to leak through between the polyvinyl tubing and the graft proper, thus coating the lumen of the graft and filling the interstices of the graft. Then, retighten the clamp for several minutes. Then again release it. At this stage it may be necessary to reinforce the suture line with an extra suture or two. When satisfied that the anastomosis is secure and that the graft is no longer leaking, a simple arteriotomy is done (either above or below the graft). The polyvinyl stent is removed, and the arteriotomy is closed.

It is obligatory in any bypass procedure to heparinize the patient and, at the termination of the operative procedure, to neutralize the heparinization effect with protamine sulfate.

The simplification of a specialized surgical procedure will permit the well-trained general surgeon to have confidence in coping with situations which may arise during the course of his surgical career, such as extensive resections or trauma involving major vessels which have to be managed properly at the time he is performing the operation.

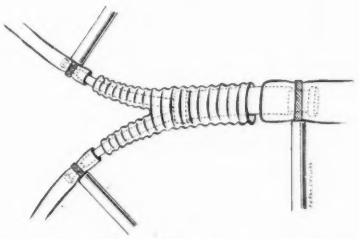


Fig. 3.—Bifurcation graft with its internal bypass.

Bifurcation Graft.—A similar principle is used (Fig. 3). Various sizes of polyvinyl bifurcation stents are prepared in advance. The stent is slipped into the permanent graft which has already been fashioned into the proper size and length to suit the replacement. The diseased segment is then resected, occluding the aorta long enough to slip the prosthesis with its bypass mechanism into place and applying three clamps. Proceed with the three anastomoses. Postclot and test these anastomoses as just described. When satisfied as to their security, perform an arteriotomy through the proximal aorta and remove the polyvinyl tube. Then close the arteriotomy.

REPLACEMENT OF ABDOMINAL AORTA REQUIRING A BRANCH OR BRANCHES

Such branches as the renal arteries, superior mesenteric artery, and celiac artery may be involved in the disease process.

While appraising and mobilizing the diseased segment, measure accurately the permanent prosthesis, such as, bifurcation of the aorta with involvement of both renal vessels so that a second team can work on it. Identify the site of the branch or branches. Construct in the operating room the polyvinyl

stent with the branch or branches and, over this, fashion the permanent prosthesis. Replace the resected specimen with the above unit holding all jointed areas together with clamps. Anastomose and follow the techniques just described.

It may be necessary at times to use a temporary branch (or branches) bypass from the aorta to a large artery, such as the renal, superior mesenteric,

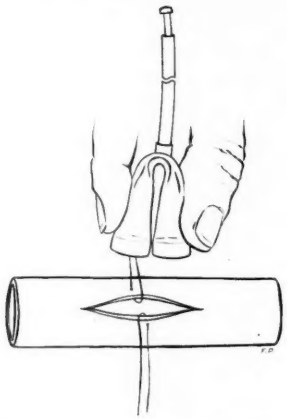


Fig. 4.—The method for rapid temporary branching of the aorta.

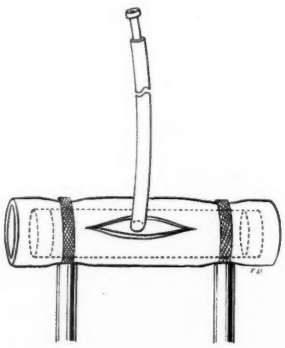


Fig. 5.—Temporary branching of aorta–completed.

or celiac vessels. This can be performed rapidly using the same principle. An incision is made into the aorta slightly larger than the folded polyvinyl stent with its branch (Fig. 4). When the fingers are released, the prosthesis, because of its elasticity, unfolds within the blood vessel. Now apply a clamp at each end (Fig. 5).

The Aortic Arch.—Here we have a different problem because of the time factor involved. The brain can tolerate only about 4 minutes of anoxia before irreversible damage takes place. It could become distinctly hazardous to attempt

to place and clamp in position within 4 minutes five anastomotic sites; namely, two aortic anastomoses, one innominate anastomosis, one left common carotid anastomosis, and one subclavian anastomosis. Therefore, a safer approach is desirable, making sure that the circulation to the brain is maintained without prolonged interruption while placing the graft with its stent, using the principles just described.

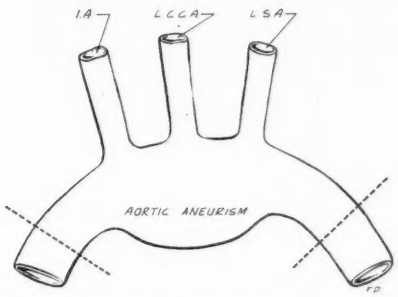


Fig. 6.—Aortic aneurysm–segment to be resected.

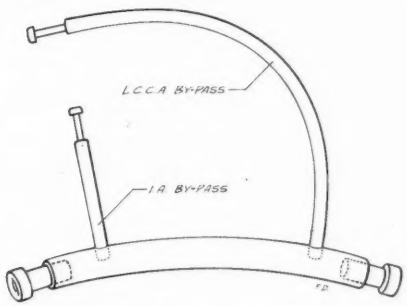


Fig. 7.—The polyvinyl prosthesis to bypass the aortic arch.

The following steps are taken when it is determined that the lesion is resectable, after it is mobilized and ready for resection.

1. (Fig. 6) Measure accurately the length of the graft (the aortic arch) to replace the resected segment, and mark on this the sites of the three branches —innominate artery, left common carotid artery, and left subclavian artery. With a circular sharp reamer cut the holes at these sites.

2. Carefully sew onto the graft the branches for the left common carotid and subclavian artery units, leaving them longer than needed so that they can be fashioned in length subsequently. The innominate artery branch, which must be accurate in length, will be sutured into place later.

3. The polyvinyl bypass (Fig. 7) will now be accurately measured, making it 1 inch longer than the permanent prosthesis on its proximal side and 2 inches longer on the distal side. To this structure, two branches are placed.

(a) At the level of the innominate artery, this branch is 1 inch longer than the accurately measured permanent prosthesis branch (Fig. 8). (b) A long branch (5 to 6 inches) is placed approximately 1 inch away from the distal part of the stent. This branch will be used to bypass subsequently the left common carotid artery.

4. Place the main polyvinyl tube within the permanent prosthesis (Fig. 8) and pull the flexible branch through the hole in the permanent prosthesis previously made for the innominate artery. Slip the accurately measured innominate artery prosthesis branch over the polyvinyl branch and then carefully suture it to the main prosthesis.

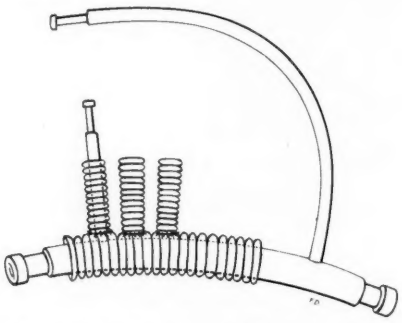


Fig. 8.—The polyvinyl prosthesis (stent) within the graft proper. Note that only the innominate artery has a polyvinyl branch in it. The unit is now ready to be placed in position within the permanent graft.

One now has a compact, wieldy, double-lumened structure ready to replace the diseased organ.

5. Apply an occlusive aortic clamp (Satinsky, Pott's, or Mueller) at each end of the aorta, and three bulldog type of clamps on the three branches. Resect the aortic arch with its branches. Immediately slip the polyvinyl innominate branch up into the distal part of the innominate artery (Fig. 9) and apply a clamp; then slip the proximal polyvinyl tube into the proximal aorta and clamp. An occlusive clamp is now applied on the distal aortic polyvinyl tube. Upon the partial release of the proximal aortic occlusive clamp, blood will at once begin to flow to the brain by way of the innominate artery.

6. Make a small incision into the distal aorta 1 inch away from its severed end (Fig. 9). Through this opening pull through the long distal polyvinyl branch and clamp the latter. Then slip the distal end of the aortic polyvinyl tube into the distal aortic segment and clamp. Now completely release the occlusive clamp previously placed on the main distal polyvinyl tube. This now permits blood to flow through the thoracic aorta.

7. Make an incision high up into the left common carotid artery (Fig. 9); into this opening, thread the long polyvinyl branch and apply a clamp to hold it in place. On removing the occlusive clamp previously placed on this branch, the brain will now receive a full, bilateral complement of blood. Now one can proceed with the various anastomoses.

8. Anastomose in the following order: (a) the proximal aortic segment, (b) the innominate artery segment, and (c) the distal aortic segment.

Test these three anastomoses for stability and porosity of the prostheses. In order to do this it is necessary first to place temporarily an occlusive clamp on the aorta distal to the distal aortic anastomosis and to pinch off the top of the aortic arch at the level of the left common carotid and subclavian arteries, using a curved nontraumatic clamp. This is followed by loosening slightly the clamp on the innominate artery, thus permitting blood to flood the entire graft in order to postclot the prosthesis and test the suture lines. Retighten the innominate artery clamp. Remove the two recently applied occlusive clamps ([1] from the distal aorta, and [2] from the left common carotid and subclavian arteries).

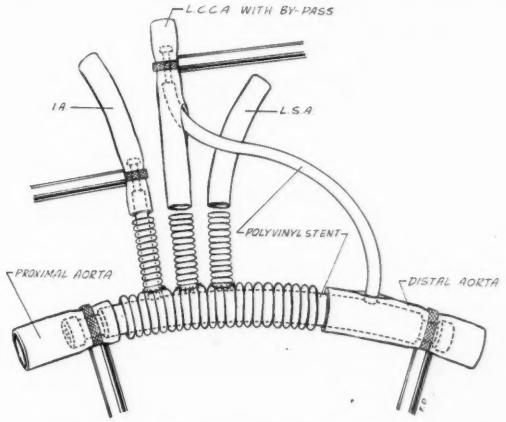


Fig. 9.—The graft and stent in place and ready for anastomosis.

After fashioning the length of the left common carotid and left subclavian segments (Fig. 9), perform an open anastomosis on each. Test the latter two anastomoses by slightly loosening the clamp on the proximal aortic anastomosis.

9. After the termination of all anastomoses (Fig. 9), and when satisfied that they are secure, occlude the left common carotid artery above its anastomotic line. Remove the polyvinyl branch from the slit in the vessel and close the arteriotomy. Then clamp this polyvinyl branch close to its origin and excise the excess tubing. Clamp the proximal aortic arch with an occlusive clamp placed proximal to the anastomosis and remove all other clamps. Enlarge the opening in the distal aorta and carefully pull out the entire bypass. There should be no difficulty with the innominate artery branch because of the flexibility of the polyvinyl tubing. Close the distal aortotomy and release the aortic occlusive clamp.

This procedure should not produce anoxic damage to the spinal cord for the circulation to the thoracic aorta is not shut off at any time for more than 1 to 2 minutes.

The same principles can also be readily applied in the management of a difficult coaretation of the aorta.

DISEASE INVOLVING THE ARTERIES TO THE BRAIN WHICH REQUIRE THEIR RESECTION AND REPLACEMENT

a. If there be intermediate segmental disease of these vessels, the procedure is relatively easy, using the principle as depicted in Fig. 2, that is, resect the segment and replace with a graft.

b. If the proximal segments of these vessels are involved, that is, adjacent to the aorta which at this point is probably also diseased and, therefore, inadequate for anastomosis, a different procedure must be attempted.

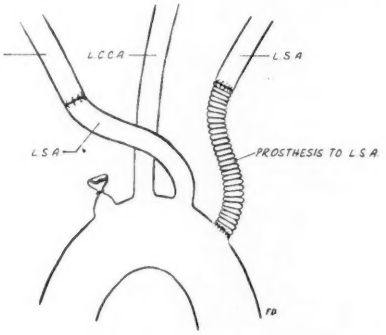


Fig. 10.—Replacement of the innominate artery with a direct graft from left subclavian artery and prosthesis replacement of proximal left subclavian artery.

If only one vessel, either the innominate artery or the left common carotid artery is so involved, first ligate this vessel at its origin from the aorta. An attempt should be made to determine if the left subclavian artery is long enough to be swung over in order to bridge it to a patent healthy portion of the involved vessel (Fig. 10). (An autograft, particularly if it is already attached to the host side, is superior to any other type of graft.)

If so, divide the left subclavian artery proximal to its vertebral branch and anastomose it (Fig. 10) to the distal portion of the above considered vessel. Then re-establish continuity of the severed left subclavian artery by means of a graft, the "take-off" of which is from a temporarily, partially occluded portion of the upper thoracic aorta.

If the left subclavian artery is not long enough, then it will be necessary to graft directly from the distal aortic arch area onto this vessel.

If both major vessels are involved close to the aorta, the chances are that the aorta itself is seriously diseased and therefore inadequate and unfavorable for anastomosis. In such event one can do one of two procedures: (1) replace the aortic arch, or (2) "tap" two areas (one at a time) distal to the arch, and bridge two prostheses to a patent portion of the vessels.

SUMMARY

A nontraumatic arterial clamp has been developed, facilitating arterial anastomosis and readily permitting rapid bypass procedures on the great vessels using the heart itself as the source of extracorporeal circulation.

REFERENCES

1. De Bakey, M. E.: Presidential Address: Changing Concepts of Thoracic Vascular Surgery, J. THORACIC SURG. 38: 145, 1959.
2. Johnson, J., Kirby, C. K., and Lehr, H. B.: A Method of Maintaining Blood Flow Through the Thoracic Aorta While Inserting an Aortic Graft to Replace an Aortic Aneurysm, Surgery 37: 54, 1955.

A METHOD OF SECURING TUBING CONNECTIONS IN CARDIOPULMONARY BYPASS EQUIPMENT

David Wyatt Aiken, M.D., Philadelphia, Pa.

MOST PUMP-OXYGENATORS have from six to twenty connections for plastic or rubber tubing, which must not leak or separate during bypass. An adaptation of the Corbin clamp, widely used in home washing machines and on auto radiator hoses, has proved satisfactory for securing tubing connections in pump-oxygenators. Six months of use in clinical and laboratory bypass programs has demonstrated the usefulness of this clamp. The modification is simple.

CURRENT METHODS

Among methods currently in use are wire and pliers, worm-tightening hose clamps, and adhesive tape. At least one company has marketed an efficient cap-screw type of clamp for each connector which provides a secure connection, but it is doubtful that their advantages warrant the additional expense. Wiring the connections is laborious and often results in minor wounds of the fingertips. Worm-tightening clamps, although satisfactory for larger tubing, have an imperfect circle of contact on ½ inch tubing, may leak under pressure, and wear out. Adhesive tape has been found satisfactory by some workers, but adherence is unpredictable between surfaces and the adhesive is difficult to remove.

CORBIN CLAMPS

Corbin clamps are adaptable in the two smallest sizes commercially available, ⅝ and ¾ inch. These (Fig. 1) are made of a highly tempered spring steel alloy and are applied with Corbin pliers which have depressions in the jaws to receive the ends of the clamp. These items are cheap, strong, and durable, and available at most washing machine repair shops. When properly fitted, Corbin clamps take less time to apply than either wire or worm-tightening clamps.

MODIFICATIONS

1. To increase the range of application, about ¼ inch has been ground off the handles of the pliers on a grinding wheel, thereby permitting tighter closure of the pliers and wider opening of the clamps.

From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania, Philadelphia, Pa.

This work has been supported in part by U. S. Public Health Grant HTS-5224.
Received for publication Jan. 28, 1960.

2. To increase the variations in sizes of tubing and connectors which these clamps will fit, clamps of each size have been enlarged slightly by grinding the inside surface. With a carborundum cone (Fig. 1, *C.C.*) placed in a drill press or other power tool and the clamp held with Corbin pliers, about one third of the thickness of the spring steel has been removed. Care has been taken to avoid overheating and loss of the steel's temper by dipping the clamp in water frequently during grinding. Because of the strength of the clamps, this procedure has not significantly altered their holding characteristics when properly fitted. From the two sizes of clamps, four sizes have been thus obtainable, designated Nos. 1, 2, 3, and 4 in ascending size.

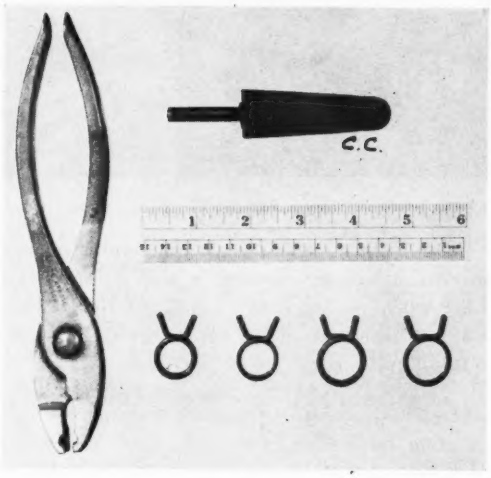


Fig. 1.

PRACTICAL APPLICATION

Combinations of applicable connector and tubing sizes are shown in Table I. With a little practice and persistence their use has become easy and the time saved has been rewarding. No failures have been observed. There has

TABLE I. SIZES OF CONNECTORS AND TUBING WHICH ARE SATISFACTORILY SECURED BY 5/8 AND 3/4 INCH CORBIN CLAMPS

CONNECTOR	TUBING		
EXTERNAL DIAMETER (INCH)	INTERNAL DIAMETER (INCH)	WALL THICKNESS (INCH)	CLAMP NO.
7/16	1/4-5/16	1/8 (rubber)	1
9/16	3/8	1/16 (plastic)	1*
	1/2	1/16 (plastic)	2†
	1/2	1/8 (rubber)	3
11/16	1/2	1/16 (plastic)	4‡

*Tubing wall is thinned by stretching in this case.
†No. 1 will do but is difficult to apply.
‡No. 3 will do but is difficult to apply.

been no leakage, slipping, separating, or breaking. To assure a tight fit, slight traction has been exerted on the tubing while the clamp was advanced over the connector. This traction stretches and thins the tubing wall momentarily.

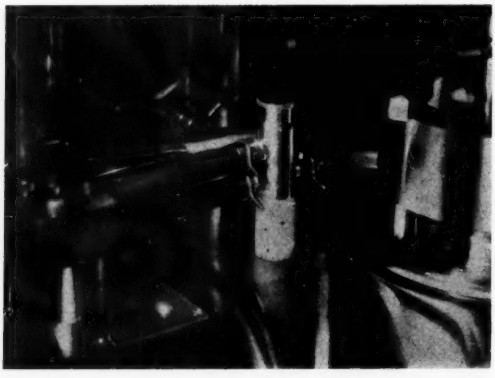


Fig. 2.

The $\frac{7}{16}$ inch metal connectors (external diameter), when used with $\frac{1}{4}$ inch rubber tubing (internal diameter) having a wall $\frac{1}{8}$ inch thick, permit slight sliding of the rubber when pulled, even though clamped. Expansile movement of the rubber tubing in this situation has not occurred, however, nor has leakage, with pressures up to 750 mm. Hg.

Fig. 2 shows the clamps in place in various locations on a pump-oxygenator.

SUMMARY

Modification and application of a simple, convenient, reliable, and economical clamp for rapidly securing tubing connections in cardiopulmonary bypass equipment have been described.

A STAINLESS STEEL Y CONNECTOR WITH VALVES FOR USE IN EXTRACORPOREAL PERFUSION WITH A ROTATING DISC OXYGENATOR

Albert H. Pemberton, M.D., Benjamin G. Narodick, M.D., and Mortimer M. Bortin, M.D., Milwaukee, Wis.

With the technical assistance of P. Beihoff, E. Balmer, and P. Durling

IN USING the various types of pump-oxygenators for extracorporeal circulation, there is a period of time just prior to the onset of bypass when it is necessary, at least momentarily, to turn off the pumping mechanism so that the venous and arterial connections to the patient can be made. Blood is thus stationary in the tubing, reservoirs, oxygenator, and filters for a variable period of time. Air trapping, fibrin deposits, pump failures, and contamination are possible during this shutdown period and may add to the risk of perfusion. In addition, with disc oxygenators employing a stationary heating element under the oxygenator for warming of the extracorporeal blood, this shutdown period permits rapid temperature buildup in the oxygenator with its attendant dangers to the corpuscular elements of the blood.

The safety factors present in an independent pump-oxygenator circuit to which the patient may be included in a leisurely fashion without pump-oxygenator shutdown have long been recognized and employed by the Mayo Clinic group utilizing a stationary screen-oxygenator.[1] The actual technique of establishing and discontinuing bypass, to be reviewed herein, is in many respects similar to the technique employed by them.

In utilizing a commercially made rotating disc oxygenator,* we have added an independent pump-oxygenator circuit by means of a Y connector† with valves incorporated as part of the end plate of the Gross arterial filter. By simultaneously opening one valve and closing the other, it is a simple matter to include or exclude the patient from the extracorporeal circuit without the potential risk of danger in the simultaneous clamping and release of appropriate lines with hemostats.

From the Cardiovascular Research Laboratory, Evangelical Deaconess Hospital, and the Departments of Medicine and Surgery, Marquette University School of Medicine, Milwaukee, Wis.

Supported by a research grant from the John A. Hartford Foundation, New York City.
Received for publication Feb. 5, 1960.

*Manufactured by the Mark Company, Randolph, Mass.

†Made by the Perlick Brass Company, Milwaukee, Wis.

DESCRIPTION OF THE Y CONNECTOR

The Y connector (Fig. 1) is made of stainless steel and is designed to fit securely by means of a special split-nut attachment (*D*, Fig. 1) to the end plate of the Gross arterial filter. Incorporated in each limb of the Y is a valve of the T-tapered barrel type (*G* and *H*, Fig. 1). The stem of the Y and one limb (*B*, Fig. 1) are of ⅜ inch internal diameter while the other limb (*C*, Fig. 1) is ½ inch internal diameter. The internal surface of the entire unit is highly polished and is constructed to eliminate dead space and turbulent flow. The

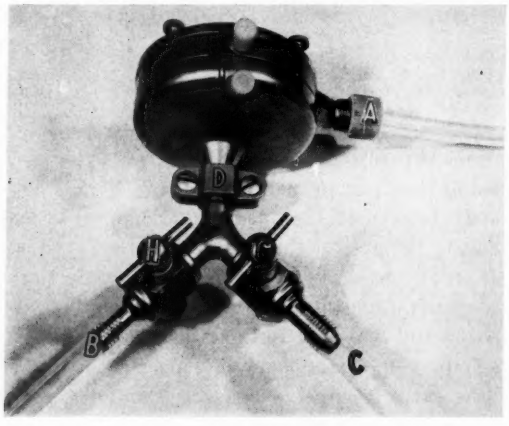


Fig. 1.—Y connector with valves (assembled).

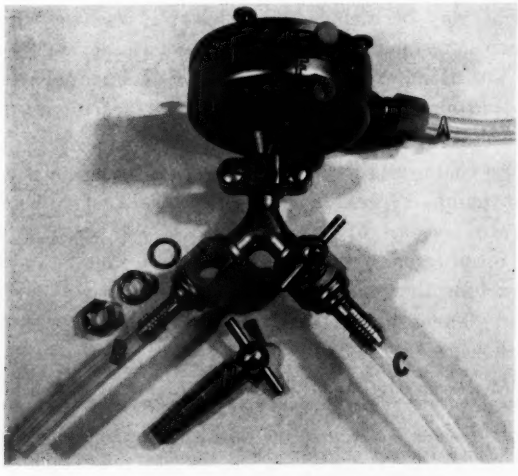


Fig. 2.—Y connector with one valve disassembled.

unit may be easily disassembled for autoclaving. Fig. 2 shows one valve disassembled. The Y has been siliconized, and a thin film of Dow Corning high vacuum stopcock grease is applied to the valveheads before inserting them into the unit during sterile assembly.

TECHNIQUE OF ESTABLISHING AND DISCONTINUING BYPASS USING THE Y CONNECTOR

By incorporating the Y unit and by appropriate connections, two circuits are established (Fig. 3). One, the independent pump-oxygenator circuit (*D*, Fig. 3), returns blood by way of the ⅜ inch Y limb to the venous reservoir completing an internal or recirculation circuit. The ½ inch limb of the Y (*C*, Fig. 3) is thus available for making the appropriate arterial connection to the patient and is covered with gauze to maintain sterility. While the chest incision is being made, the pump-oxygenator is primed with blood at 37° C. which is slowly recirculated through the pump-oxygenator circuit on room air. After

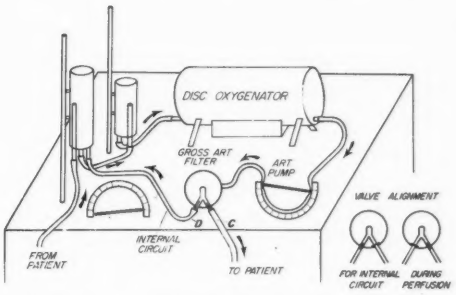


Fig. 3.—Diagram of the circuits established by the Y connector.

the patient is heparinized and while the arterial cannula is being placed, each end of a 12 to 14 foot length of sterile Tygon tubing (½ inch internal diameter) is handed back by the operating surgeon to the pump operator who attaches one end in an aseptic fashion to the ½ inch limb of the Y and the other end to the appropriate inlet of the venous reservoir. Following oxygenation of the slowly recirculating priming blood, the valves are turned to the perfusion position (Insert, Fig. 3), and the Tygon "loop" is completely filled with oxygenated blood in a manner which forces out all air. As the surgeon doubly clamps the "loop" at its mid-point, the pump operator simultaneously returns the valves to the internal circuit position (Insert, Fig. 3), and recirculation continues again on room air. The filled loop is divided between the clamps and, by means of specially designed arterial and venous connectors,* airfree connections are made to the arterial and venous cannulae. Before inserting the superior vena cava cannula, which is the last step prior to instituting bypass, the pump operator again oxygenates the recirculating blood. Perfusion is begun by returning the valve alignment to the perfusion position and turning up the speed

*Available from V. Mueller Company, Chicago, Ill.

of the arterial pump to the proper level. Perfusion is discontinued by turning the valve alignment to the internal circuit position after which recirculation is continued by the pump operator in a standby fashion. It is a simple matter to re-establish bypass should this be necessary.

On occasion, early in our laboratory experience, mishaps, such as arterial line blow-offs, have made this Y connector a lifesaving device. The interior of the Y unit has been repeatedly examined following extracorporeal procedures. On no occasion has there been evidence of clotting or fibrin formation.

SUMMARY

A stainless steel Y connector with valves has been designed for a rotating disc oxygenator on the end plate of the arterial filter to permit the unhurried establishment and discontinuance of whole body perfusion. The simplicity and safety factors inherent in this technical modification, with particular reference to the disc oxygenator with a stationary heating plate, are discussed.

REFERENCE

1. Jones, R. E., Donald, D. E., Swan, H. S. C., Harshbarger, H. G., Kirklin, J. W., and Wood, E. A.: Apparatus of the Gibbon Type for Mechanical Bypass of the Heart and Lungs, Preliminary Report, Proc. Staff Meet. Mayo Clin. **30**: 105-115, 1955.

A SIMPLE METHOD FOR STARTING THE SIPHONAGE OF BLOOD FROM VENAE CAVAE DURING MECHANICAL BYPASS

Gerónimo N. Guastavino, M.D., Jaime A. Wikinski, M.D., Raúl H. Andrés, M.D., Jorge E. Quinterno, M.D., and Carlos A. Donadei, M.D., Buenos Aires, Argentina

ONE of the basic conditions of extracorporeal circulation is to replace, through the arterial pump, the exact volume of blood diverted from the body.

The perfusion flow will depend largely on the volume of blood drained through both venae cavae. The factors which may modify this volume are (1) the recipient's systemic pressure, (2) the internal diameter of the caval catheters, and (3) the pressure gradient between the venous reservoir and both venae cavae.

The three methods to produce enough gradient to remove blood are suction, siphonage, and suction plus siphonage. We have used all of these methods and found that siphonage, as reported by other surgeons, to be the easiest and simplest method.

To start the siphonage it is necessary to have the plastic tube which connects caval catheters with the venous reservoir filled with a liquid column. (We use a disc oxygenator of the Kay-Cross type.) To fill this tube with blood we first used the following methods with indifferent success.

1. Before connecting the venous tube to the caval catheters we lowered the level of this tube and filled it with the blood from the reservoir oxygenator. Then we clamped the tube and connected it with the caval catheters. Releasing the tube's clamp starts the siphonage. This method has the inconvenience that to be reproduced it is necessary to disconnect the venous tube from the caval catheters.

2. We filled the venous tube directly with blood removed through the caval catheters. This was easier to do when the venous tube used was of an internal diameter (ID) of a ¼ inch (6.35 mm.), but difficult when we used tubes ½ inch (12.7 mm.) in diameter. The problem was to remove all the air from the tube with the consequent delay in the withdrawal of the blood from the venae cavae.

From the Experimental Section of Cardiovascular Surgery, Instituto Argentino de Diagnóstico y Tratamiento, Buenos Aires.

This work was supported by The Williams Foundation.
Received for publication Feb. 2, 1960.

To start the siphonage effectively at the beginning of the pump run it is necessary to have the venous tube completely filled, and to be able to refill it in a few seconds if necessary.

METHOD

The following method is being used by our group with satisfactory results. A lateral tube (of 2 mm. ID) was added to the Y connector used to fix the caval catheters to the venous tube (Fig. 1, *A*). This new tube is connected by a plastic tube with a negative pressure of 50 cm. of water, the same negative pressure used in our machine to produce suction in the coronary reservoir. After the caval catheters (Fig. 1, *B*) are in place (with a clamp closing its free end), they are connected to the venous tube (Fig. 1, *C*) by the Y connector. The venous tube in our machine connects the caval catheters to the reservoir oxygenator (Fig. 1, *D*).

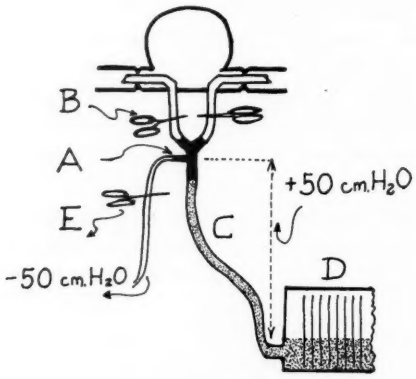


Fig. 1.

The clamp closing the plastic lateral tube of the Y connector (Fig. 1, *E*) is then opened, allowing the blood of the reservoir oxygenator to fill the venous tube, sucked into it by the negative pressure already mentioned. Then this lateral tube is closed and blood remains in the venous tube until the caval catheter clamps are opened, thereby starting the siphonage.

This quick and safe maneuver is performed in less than 10 seconds, and may be repeated if necessary. We have used this procedure in the last 18 experimental and in 2 clinical bypass procedures with gratifying results.

ADDENDUM

May 27, 1960.—At this time the authors are using the same principle but two separate tubes from each caval catheter to the oxygenator. The suction is then made in each connector between the catheter and the tube.

Nov. 21, 1960.—By this date, 11 patients have been operated upon.